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DEDICATED TO THE HEALTH OF ALL CHILDREN®

Emphasis on the First Syllable

Joseph A. Zenel, MD
Editor-in-Chief, Pediatrics in Review
Sanford Children's Hospital, The Sanford School of Medicine,
University of South Dakota, Sioux Falls, SD

"Emphasis on the first syllable. Rhymes with kennel." This is my well-seasoned response when asked how to pronounce my last name. At the start of each school year when our children were growing up, our children would annually complain at the dinner table about how badly our last name was pronounced by the new teacher. Invariably our children would follow with, "Yeah, we know Dad! Emphasis on the first syllable. Rhymes with kennel."

My last name used to be longer and significantly more nuanced in pronunciation. Family legend has it that my paternal grandfather, fleeing from World War I, emigrated from Poland at age 14 years and could not write or spell his last name in English. On arrival in the United States, the coal mining company that hired him signed his last name with the single letter *Z*. My grandfather went directly to work, did not go to high school or college, and, unfortunately, died before I was born. Family legend also states that when my father went to school, either the administration or my father changed our family's last name to make it easier for others to spell and pronounce. (Unfortunately, when he changed the name by placing a single *n* in the middle, he did not realize that most people on first glance would emphasize the second syllable on pronunciation.) College was out of the question for my father when he graduated from high school; he worked as an accountant for a brewery, but was soon drafted when the United States entered World War II. Thanks to the post-war GI Bill, my father received a college education, which, in turn, led to opportunities, a successful career, a family, my birth, my medical education, and me becoming a pediatrician.

According to the Online Merriam-Webster Dictionary, pediatrics is "a branch of medicine dealing with the development, care, and diseases of infants, children, and adolescents." (1) The word *pediatrics* derives from the Greek words *pais*, which means child, and *iatros*, which means doctor or healer. As pediatricians, our charge is that first syllable, *ped*. As pediatricians, we strive to provide an environment best suited for a child's optimal development. As pediatricians, we care for all children from all backgrounds.

The mission of the American Academy of Pediatrics (AAP) is "to attain optimal physical, mental, and social health and well-being for all infants, children, adolescents and young adults. To accomplish this, AAP shall support the professional needs of its members." (2) One professional need is education, through which we better ourselves and the children we care for. *Pediatrics in Review*, an American Academy of Pediatrics peer-reviewed journal, enters its 40th year of publication. From its inception, *Pediatrics in Review* has been dedicated to educating pediatricians on current, evidence-based, relevant knowledge crucial for the practice of pediatrics throughout the world.

AUTHOR DISCLOSURE Dr Zenel has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

I am both honored and proud to be a pediatrician and the editor-in-chief of *Pediatrics in Review,* and I am very fortunate that I grew up in a place that offered opportunities for personal growth and achievement, a place my grandfather sought at great risk to his life. All I have of my grandfather's possessions is his coal mining pickaxe, the head of which displays a shallowly engraved *Z*. I often imagine a lonely, scared, 14-year-old, adolescent boy scratching *Z* on that rough-surfaced tool as he wondered how to survive in a new country. What he did reminds me that as pediatricians we are dedicated to helping all children in need, especially those from very disadvantaged backgrounds. While I remind others to place the emphasis on the first syllable when pronouncing my last name, I also remind our readers that *Pediatrics in Review,* as it enters its 40th year of publishing, places and will continue to place its emphasis on that "first syllable" in pediatrics: the infant, the child, and the adolescent.

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Joseph A. Zenel

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Sleep-Disordered Breathing in Children

Kevin Gipson, MD, MS,* Mengdi Lu, MD,* T. Bernard Kinane, MD*

**Division of Pediatric Pulmonology and Sleep Medicine, Department of Pediatrics, Massachusetts General Hospital for Children and Harvard Medical School, Boston, MA*

Practice Gaps

An estimated 1% to 5% of children have sleep-disordered breathing related to obstructive sleep apnea, with a smaller proportion of children having central or mixed sleep apnea. Improved screening for sleep-disordered breathing in the general pediatrics clinic, coupled with effective management strategies, has the potential to have wide-ranging benefits on the patient's long-term health and development.

Objectives

After completing this article, readers should be able to:

1. Recognize the signs and symptoms of obstructive sleep apnea in pediatric and adolescent patients.
2. Understand the role of in-laboratory sleep studies in the evaluation of pediatric patients with suspected sleep-disordered breathing.
3. Weigh the indications, benefits, and risks of various therapies for obstructive sleep apnea.
4. Have a general understanding of, and maintain an appropriate index of suspicion for, comorbid central sleep apnea when a patient presents with signs of sleep-disordered breathing.

AUTHOR DISCLOSURE Drs Gipson, Lu, and Kinane have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
AHI	apnea-hypopnea index
AT	adenotonsillectomy
Bi-level	bilevel positive airway pressure
CPAP	continuous positive airway pressure
CSA	central sleep apnea
FDA	Food and Drug Administration
OSA	obstructive sleep apnea
PAP	positive airway pressure
PSG	polysomnography
SDB	sleep-disordered breathing

INTRODUCTION

Sleep is central to a healthy childhood, and sleep-disordered breathing (SDB)—the disruption of normal respiratory patterns and ventilation during sleep—is implicated in several behavioral and physical health issues. Although we now have strong evidence that chronic, unchecked obstructive sleep apnea (OSA) can lead to hypertension, cardiovascular disease, metabolic disorders, obesity, and neuropsychiatric and developmental issues, the full scope of the effect of SDB on health remains underappreciated by many clinicians (Table 1).

Sleep research has rapidly expanded and evolved in the past few decades. Of recent note, chronobiologists Hall, Rosbash, and Young received the 2017 Nobel prize in medicine for their work on the cell's internal clock. While the biological role of sleep remains mysterious, as famed researcher Allan Rechtschaffen once remarked, "If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made." Intriguing new research

TABLE 1. Disease States Associated with or Complicated by Chronic Sleep-Disordered Breathing

SYSTEM	DISEASE STATE
Cardiovascular	Hypertension
	Pulmonary hypertension, cor pulmonale
Pulmonary	Bronchopulmonary dysplasia
Hematologic	Sickle cell disease
Nutrition and metabolic	Obesity
	Insulin resistance
	Failure to thrive (malnutrition)
Neuropsychiatric	Attention-deficit/hyperactivity disorder
	Major depressive disorder
	Developmental delay

has begun to suggest concrete mechanisms by which sleep maintains health, including the diurnal clearance of toxic central nervous system metabolites. (1) In another striking example of the central role of sleep on health, recent research suggests that telomere length, a marker of a chromosome's viability and a proxy for aging, is significantly shortened in children with chronically insufficient sleep. (2)

Sleep-disordered breathing is common, with the American Academy of Pediatrics (AAP) Subcommittee on Pediatric Sleep estimating that 1.2% to 5.7% of children are affected by OSA alone. (3) It is generally acknowledged that this may be an underestimate of the true prevalence, and it is widely believed among sleep experts that the incidence of OSA in the pediatric and adolescent populations is increasing in the United States as a consequence of the childhood obesity epidemic. Affected children are at risk for wide-ranging direct health consequences from sequelae of OSA, including the impact of insufficient sleep on the development or exacerbation of chronic disease. Beyond the physical and mental health effects of SDB on the child, disrupted or disordered sleep can be a major psychosocial stressor for children and their families. (4) As such, effective screening for SDB in the general pediatric and adolescent medicine clinics can have a significant effect on the health and well-being of children and their families. The general pediatrician should feel empowered to identify SDB in their patients (Table 2).

OBSTRUCTIVE SLEEP APNEA

Introduction

A variety of physiologic changes occur during the normal transition to sleep, including relaxation of upper airway tone and a decrease in respiratory tidal volumes. (5) However, in patients with OSA, airflow is severely reduced or even entirely blocked during sleep by an abnormality of the upper airway anatomy, most commonly adenotonsillar hypertrophy. Obstructive sleep apnea in the pediatric population is defined as either frank obstruction or evidence of hypopnea

TABLE 2. American Academy of Pediatrics 2012 Guideline Recommendations for the Diagnosis and Treatment of OSA in Children and Adolescents (3)

1. All children/adolescents should be screened for snoring.
2. Polysomnography should be performed in children/adolescents with snoring and symptoms/signs of OSA; if polysomnography is not available, then alternative diagnostic tests or referral to a specialist for more extensive evaluation may be considered.
3. Adenotonsillectomy is recommended as the first-line treatment for patients with adenotonsillar hypertrophy.
4. High-risk patients should be monitored as inpatients postoperatively.
5. Patients should be reevaluated postoperatively to determine whether further treatment is required. Objective testing should be performed in patients who are high risk or have persistent symptoms/signs of OSA after therapy.
6. Continuous positive airway pressure is recommended as treatment if adenotonsillectomy is not performed or if OSA persists postoperatively.
7. Weight loss is recommended in addition to other therapy in patients who are overweight or obese.
8. Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA

OSA=obstructive sleep apnea.

or obstructive hypoventilation on a sleep study, occurring in the context of a history of snoring, labored breathing during sleep, daytime sleepiness, or learning and behavioral issues (Tables 3 and 4). As a consequence of these obstructive events and subsequent arousals, children and adolescents with OSA may have reduced sleep quality, resulting in behavioral issues, poor school performance, or daytime sleepiness.

An understanding of the adverse health effects of and therapies for the management of OSA have greatly evolved since Guilleminault, Eldridge, and Dement first described the pediatric OSA syndrome in the early 1970s. In this early report, 2 of 8 patients in the case series had marked OSA with severe comorbid hypertension, which resolved after tracheostomy. (6)(7)(8) Fortunately, in current practice, most cases of even extreme OSA are amenable to less invasive forms of therapy. There is now ample evidence of both adverse cardiac and autonomic effects of chronic OSA, including correlations with systolic and diastolic hypertension, tachycardia, and increased heart rate variability. (3) A variety of psychological and neuropsychiatric studies have clearly linked OSA to learning and attention deficits and behavioral issues. This is in contrast to adults with OSA, where the main symptom is daytime sleepiness. Happily, emerging evidence suggests that some of these impairments may be mitigated by effective OSA treatment. (3)

Today, in conjunction with adenotonsillectomy (AT) and other interventions, a variety of sophisticated devices for the delivery of positive airway pressure (PAP) permit effective management of OSA. However, significant discrepancies in the delivery of care to these patients remain, and there is evidence that OSA may disproportionately affect children from socioeconomically disadvantaged backgrounds, even after correcting for previously established risk factors such as obesity and prematurity. (9)

Clinical Features of OSA in Pediatric Patients

History. A focused sleep history, guided by an understanding of the most common sleep disorders of childhood, can be a quick and high-yield addition to the pediatrics clinic visit. Generally, such a history will start with general questions regarding the parents' or child's perception of their sleep quality, followed by more specific questions regarding the nature of any reported sleep disturbance.

Parents will commonly not mention concerns about their child's sleep issues if not asked directly. When prompted, parents will often report snoring in their children but will frequently qualify this observation as occurring exclusively when their child is congested or with an upper respiratory tract infection. Stertor (heavy inspiratory snoring) with nasal congestion is quite common in practice and, in and of itself, does not mandate a sleep study. However, further probing questions should be asked to ascertain whether the child has any other signs of sleep disturbance, particularly signs of respiratory difficulty or apnea during sleep, and daytime concerns about school performance, behavior, focus, and sleepiness. Patients with snore concerning for OSA will generally have symptoms of audible snore 3 or more nights a week outside of the context of upper respiratory tract infections.

When parents are able to describe the concerning nocturnal breathing patterns in detail, they may describe snoring punctuated by episodes of frank obstruction or pauses in the child's breathing. Older children and adolescents may describe waking from sleep due to cough or with a panicked, choking sensation. Parents may observe visibly labored breathing accompanying pronounced snoring, including stertor, gasps, retractions, or apnea. These witnessed overt apneas are often described as "choking." However, in many children, OSA manifests as hypopneas or obstructive hypoventilation, which may not be obvious to parents. Indeed, hypopneas are quite characteristic of pediatric SDB, which is in distinct contrast to adults with OSA, who often demonstrate frank obstruction.

There may be other subtle signs of symptomatic OSA. Children may habitually sleep in positions that minimize obstruction, including with several pillows, or perhaps

TABLE 3. **Diagnostic Criteria for Pediatric Obstructive Sleep Apnea**

A. The presence of ≥1 of the following:	1. Snoring 2. Labored, paradoxical, or obstructed breathing during the child's sleep 3. Sleepiness, hyperactivity, behavioral problems, or learning problems
B. Polysomnography demonstrates 1 or both of the following:	1. One or more obstructive apneas, mixed apneas, or hypopneas per hour of sleep *OR* 2. A pattern of obstructive hypoventilation, defined as ≥25% of total sleep time with hypercapnia ($PaCO_2 > 50$ mm Hg) in association with ≥1 of the following: snoring, flattening of the inspiratory pressure waveform, or paradoxical thoracoabdominal motion

Criteria A and B must be met.

Reprinted with permission from The International Classification of Sleep Disorders. *3rd ed.*

TABLE 4. **The Spectrum of Pediatric Obstructive Sleep-Disordered Breathing**

Primary snoring	Habitual snoring >3 nights per week *without* apneas, hypopneas, frequent arousals, or gas exchange abnormalities (prevalence, 7.45%)
Upper airway resistance syndrome	Snoring, increased work of breathing, and frequent arousals *without* recognizable obstructive events or gas-exchange abnormalities
Obstructive hypoventilation	Snoring plus elevated end-expiratory carbon dioxide partial pressure in the absence of recognizable obstructive events
OSA syndrome	Recurrent events of partial complete upper airway obstruction (hypopneas, obstructive or mixed apneas) with disruption of normal oxygenation, ventilation, and sleep patterns (prevalence, 1%–5%)

OSA=obstructive sleep apnea.
Courtesy of Catherine Kier, MD, FAAP, FCCP, DABSM, AE-C, of Stony Brook Children's Hospital.

prone or with their neck hyperextended. (3) Older children with clinically significant OSA may present with daytime sleepiness as a core concern. The Epworth Sleepiness Scale for Children and Adolescents is a helpful quantitative and trackable assessment of daytime sleepiness. (10)(11) In addition to daytime sleepiness, the clinician should also screen for behavioral and learning issues, particularly regarding classroom performance. Children with marked nocturnal hypoventilation may report morning headache, which is related to carbon dioxide (CO_2) retention. Nocturnal secondary enuresis, defined as nighttime incontinence, which emerges after at least 6 months of continence, is also suggestive of SDB. (12)

A child's medical history may also inform the pediatrician's focused sleep assessment. Obstructive sleep apnea is prevalent in children with a history of prematurity. Children with chronic lung diseases, including bronchopulmonary dysplasia, are more likely to have comorbid SDB. (13) Children with neuromuscular diseases are intrinsically at risk for nocturnal hypoventilation and decreased airway tone. (5)(14) Patients with syndromes associated with macroglossia (eg, trisomy 21 and Beckwith-Wiedemann syndrome), micrognathia (eg, Pierre-Robin sequence), or palatal abnormalities may be anatomically predisposed to upper airway obstruction. (15)(16) In children with severe gastroesophageal reflux or aerodigestive issues, reflux and subclinical aspiration during sleep may mimic the "choking" sometimes observed with obstructive events and may contribute to lung disease and nocturnal hypoxemia. Patients with a history of sickle cell disease are at increased risk for disordered nocturnal breathing and are uniquely susceptible to nighttime oxygen desaturations attendant to severe OSA. (17) Any pediatric sleep history also should include screening for safe sleep practices, particularly for infants.

Physical Examination. The physical examination of the patient with suspected OSA is most effective when informed by an understanding of the myriad ways in which subtle abnormalities of a child's dentition, mandible, tongue, adenoid tissue and tonsils, and hard and soft palate interplay to contribute to an upper airway obstruction. When asleep, the muscles suspending the soft palate relax, as does the tongue. When the patient sleeps supine, these tissues may largely obstruct the upper airway. Ideally, the oropharyngeal examination should note both the Mallampati classification and the tonsillar size, as both are associated with severity of OSA (Fig 1). (18) The presence of tonsillar hypertrophy should be assessed by using a standard Brodsky scale from 0 to 4, wherein a score of 0 indicates the surgically induced absence of all tonsillar tissue and 4 indicates extension of the tonsils to the midline (so-called kissing tonsils). A high-arched palate may distort the architecture of the associated oropharynx and cause reduced nasal airflow. (5) Retrognathia or micrognathia reduces the space wherein otherwise normally sized tongue and soft tissues rest in the oropharynx. Malocclusion of the teeth may act in a similar way, forcing the jaw posteriorly and functionally reducing space in the mouth. The nasal passages should be assessed for polyps or allergic rhinitis, which can exacerbate chronic nasal congestion. The adenoidal tissue, a midline aggregation of lymphoid tissue in the upper oropharynx, is generally not observable by standard clinical examination and is best assessed via flexible nasopharyngoscopy.

Truncal obesity, redundant neck tissue, and other signs of metabolic syndrome or insulin resistance, such as acanthosis nigricans, suggest obesity-related OSA and comorbid metabolic disease. (19) Conversely, in very young infants OSA is often associated with failure to thrive, as the work of breathing required to overcome the obstruction can quickly burn calories. The thoracic cage and sternum may be visually

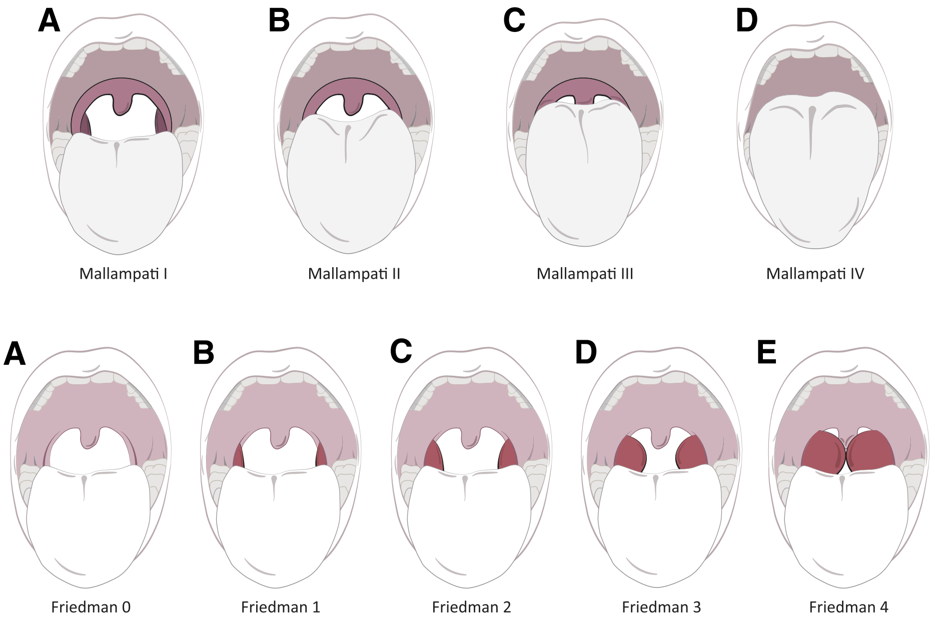


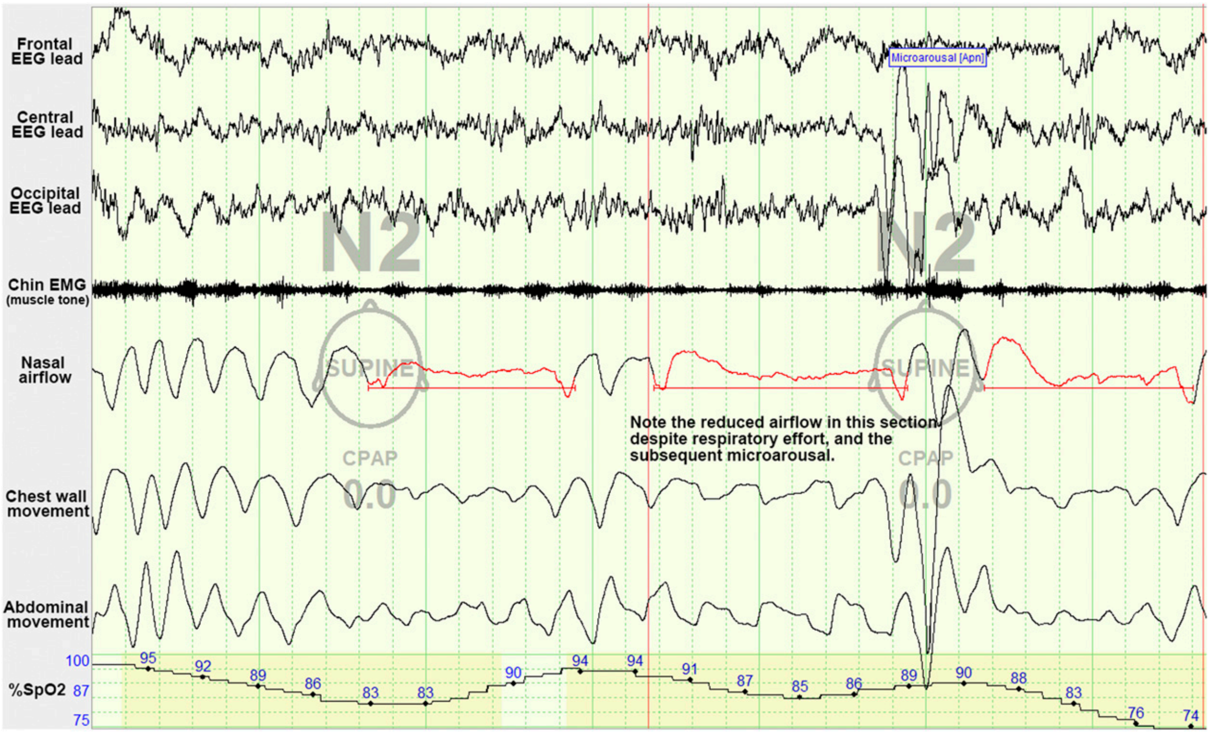
Figure 1. Mallampati score and Friedman tonsil scale. The Mallampati score, although principally intended to help estimate the relative difficulty of intubation in preoperative patients, is also useful in assessing the contribution of the upper airway anatomy to obstructive sleep breathing. The Friedman tonsil scale is useful for describing the size of tonsils in children, with a score of 0 representing surgically removed tonsils and a score of 4 describing large tonsils that meet at the midline. Image courtesy of Namrita Jain, MD.

examined for signs of pectus excavatum or carinatum, or other malformations. These changes in thoracic structure may impinge on the mechanics of ventilation and predispose a patient to obstructive hypoventilation. Signs of neuromuscular disease, such as decreased tone, Gower sign, and calf hypertrophy, should be assessed. Clubbing of the fingertips, which is often related to chronic hypoxemia and hypoventilation, may indicate underlying lung disease. In patients with established, long-term PAP use, examination of the nasal bridge for erythema, ulceration, or deformation is important to ensure appropriate mask fit. Blood pressure screening should be included in clinic triage vitals, and hypertension should be investigated when found.

Diagnosis of OSA

Basic Polysomnography. The in-laboratory sleep study, or polysomnography (PSG), is the gold standard in the diagnosis of SDB in children. The PSG informs the care of patients with clinically suspected SDB. It is most effective when paired with the clinician's history and physical examination to guide the supervising sleep physician and sleep technologists in designing and interpreting the study. On PSG, obstructive apneic events in children are defined as a decrease of airflow (as measured by a nasal flow detector) by 90% or more despite a respiratory effort for the duration of 2 breaths (Table 3, Fig 2). Hypopneas are lower-magnitude diminutions of airflow, between 30% and 90%, which are nevertheless associated with oxygen desaturations or arousal. (20)

A full pediatric sleep study in an American Academy of Sleep Medicine–accredited laboratory includes monitoring of several physiologic parameters throughout the course of an evening. In very young infants, "nap" sleep studies during the day may also be adequate. For a typical sleep study, the child and parent arrive at the sleep laboratory in the early evening. After the child acclimates to the sleep room, various leads, bands, and nasal flow sensors for data collection are attached to the patient. The room is designed to be cool and quiet, in emulation of an ideal sleeping arrangement. Parents are generally encouraged to stay overnight with young children on a nearby cot or sleeper chair. The child is monitored throughout the evening by a certified sleep technician, who observes the tracings from 1 or more patients in a central control room. Should the patient exhibit severe desaturations, prolonged hypercapnia, worrisome electrocardiographic tracings, or evidence of previously unidentified seizure activity, the sleep technician is trained to identify these issues and consult the on-call supervising sleep physician for guidance in intervention. In some cases, a "split" sleep study is conducted in which half the night is used for a standard diagnostic sleep study followed by the addition of a therapeutic intervention, typically PAP, for the remainder of the evening, which is aimed at titrating the new therapy and demonstrating efficacy. Generally, an initial sleep study should not be used for the initiation of mask-delivered PAP, particularly in very young children who are likely to be frightened by the modality and the



Note the reduced airflow in this section despite respiratory effort, and the subsequent microarousal.

Figure 2. Example of obstructive sleep apnea as seen on polysomnography. In this example of 2 obstructive sleep apnea events, note the dampening of airflow tracings with ongoing evidence of respiratory effort as seen in the thoracic and abdominal tracings. CPAP=continuous positive airway pressure, EEG=electroencephalogram, EMG=electromyography. Image courtesy of Ellen Grealish, RPSGT, R.EEG T.

unfamiliarity with the sleep laboratory environment. Although standard practice in the adult population, the use of in-home sleep studies is not recommended in the diagnosis of OSA in patients younger than 18 years of age, according to the most recent American Academy of Sleep Medicine position statement. (21) In-laboratory PSG remains the standard of care for these patients. Home oximetry is likely not sufficient for the diagnosis of OSA but may be informative in settings in which full PSG is unavailable. (22)

The resultant sleep study is staged by a technologist, a process wherein the various phases of sleep are identified and respiratory events such as obstructions are noted. A sleep physician then interprets the study, generating a summary report and communication with the ordering provider, describing the general quality and architecture of the patient's sleep. The resultant apnea-hypopnea index (AHI) reflects a combination of obstructive events, central apneas, and hypopneas and is reported as an average number of events per hour (see Table 5 for typical pediatric cutoff values). Of note, even a low AHI can cause significant impairment in children; the developing child is exquisitely sensitive to OSA.

Drug-Induced Sleep Endoscopy. Drug-induced sleep endoscopy is performed by specialists who fully understand the upper airway anatomy dynamics contributing to OSA in the sleeping patient and is particularly useful in those with persistently elevated AHI after AT. (23) Sleep endoscopy serves to define the level of the obstruction and may reveal sleep state–dependent laryngomalacia or palatine collapse, facilitating more targeted intervention from the otolaryngologist. Successful sleep endoscopy requires precise titration of anesthesia from an experienced anesthesiologist because the goal is emulation of the sleep state without obscuring the patient's actual upper airway dynamics by inducing too deep a sleep state.

Imaging and Laboratory Studies. In some cases of suspected OSA it may be beneficial to obtain lateral neck films to demonstrate upper airway narrowing. In patients with complex craniofacial abnormalities, computed tomography with three-dimensional reconstruction can be a powerful tool for oromaxillofacial surgical consultants in staging and planning interventions. (24)(25) Although there is currently a great deal of research in identifying effective biomarkers for OSA, there are presently no clinically available laboratory tests that are sensitive and specific for the disorder. (26) An early-morning blood gas may be informative in screening for nocturnal CO_2 retention. Similarly, in clinical settings equipped with end-tidal or transcutaneous CO_2 monitoring, this can be helpful in cases where chronic hypoventilation is

TABLE 5. **Classification of Sleep Apnea Severity in Children Based on the AHI**

	AHI, NO. OF EVENTS PER HOUR	
SEVERITY	**PEDIATRIC**	**ADULT**
Normal	≤1	≤5
Mild	1 to ≤5	5 to ≥15
Moderate	>5 to ≤10	>15 to ≤30
Severe	>10	>30

AHI=apnea-hypopnea index.
Adapted with permission from Dehlink E, Tan H-L. Update on paediatric obstructive sleep apnoea. J Thorac Dis. *2016;8(2):224–235.*

a clinical concern, including in obesity-related hypoventilation or respiratory insufficiency due to neuromuscular disease. In rare cases in which a previously undiagnosed neuromuscular disorder or syndrome is suspected, referral to a specialist for targeted genetic screening should be considered. Generally, pulmonary function testing is not indicated for the evaluation of SDB; however, full pulmonary function tests can provide important information when there is a concern for underlying restrictive lung disease or a diffusion defect that may exacerbate OSA.

Treatment of OSA

Lifestyle Modification. Pediatric obesity, a worsening public health issue in the United States, is an independent risk factor for OSA. For patients in whom obesity is considered a likely driver of obstructive SDB, a trial of lifestyle and dietary modification is often worthwhile, and the aid of a nutritionist can be particularly helpful in these cases. It is fairly common to see improvement in the AHI with 5% to 10% weight loss. (19) Furthermore, longer sleep duration is associated with improved measures of healthy bodyweight, and so optimal control of OSA could help patients to lose weight. (27)

Noninvasive PAP. Positive airway pressure has long been a mainstay of noninvasive management in OSA, with the first successful use in children as a tracheostomy-sparing modality described by Guilleminault et al in 1986. (28) Continuous PAP (CPAP) delivers a single set pressure to patients. This pressure is optimally set during a CPAP titration study in the sleep laboratory, wherein pressure is gradually up-titrated until resolution of the obstructive or hypopneic events is observed in real-time. Bi-level PAP (Bi-level) provides different inspiratory and expiratory airway pressures, which may be better tolerated in patients because the lower expiratory PAP permits easier exhalation. Modern CPAP devices may be equipped with an expiratory pressure release mode, which emulates Bi-level by dropping the CPAP pressure by some amount (typically 2–3 cmH_2O) during exhalation. Good mask fit is crucial to delivering appropriate pressures in CPAP and to fostering long-term patient adherence, and mask leak is recorded by most modern units for use in troubleshooting. Another important comfort consideration in children includes the use of a "ramp" with modern PAP units. A pressure ramp instructs the CPAP or Bi-level unit to slowly increase pressure over time so that the patient does not experience the full force of the PAP device until they are fully asleep. PAP is generally delivered via nasal or oronasal masks in children; however, very small infants may require the use of a next-generation nasal cannula because standard pediatric masks may be too large. Nonadherence to PAP is a common complication in both pediatric and adolescent patients. Behavioral therapy may be beneficial in acclimating patients to the mask in young children and in fostering long-term adherence. (29)

Pharmacologic Management. There are presently no Food and Drug Administration (FDA)–approved medications for the treatment of OSA in children. Montelukast, a leukotriene receptor antagonist used as an adjunctive therapy in persistent asthma, may have some benefit in OSA in which tissue inflammation (particularly of the adenoid tissue) contributes to the obstruction. In select patients, nasal corticosteroids combined with montelukast may be helpful by similarly reducing tissue inflammation and swelling in the nasal passages and adenoids, which can contribute to airflow resistance. (30) In some patients with extreme PAP mask intolerance, which may be due to sensory aversions or claustrophobia, judicious and careful use of anxiolytics or mild sedatives may be warranted, as mask aversion is a major driver of PAP nonadherence in the pediatric population. (31) Some patients with severe SDB and nocturnal hypoventilation may benefit from supplemental oxygen therapy. Although oxygen does not alleviate the mechanical ventilatory problem inherent in OSA, it may serve to minimize nocturnal hypoxemia and its effects on intellectual development and cardiopulmonary health.

Surgical Management. Adenotonsillectomy is the first-line treatment in the management of OSA in children with adenotonsillar hypertrophy. The Childhood Adenotonsillectomy Trial demonstrated improvement in PSG metrics, as well as behavioral and quality of life secondary outcomes, in both obese and nonobese children with PSG-diagnosed OSA without prolonged oxyhemoglobin desaturation. (32) Although no surgical procedure is without risks, AT is generally safe and well-tolerated, even in obese pediatric patients. (33)

One important consideration to counsel parents about when referring for AT is the possibility of reaccumulation of adenoidal tissue, which occurs in 1.3% to 26% of patients and may require subsequent surgical revision. (34) Patients with severe OSA before AT, or with persistent comorbid obesity, may benefit from follow-up PSG to confirm resolution of OSA. (3) Residual OSA, albeit to a lesser degree, persists after AT in up to 50% of patients; vigilance for recurrence of symptoms is recommended. (35) Patients who are at particular risk for residual OSA after AT include those with craniofacial abnormalities and Mallampati class III and IV airways.

There are unique management considerations in certain patient populations. The AAP guidelines suggest that children with cardiac abnormalities, specifically left or right ventricular hypertrophy, be monitored inpatient postoperatively because they have an increased risk of respiratory complication after AT. (3) Tongue debulking is occasionally used in patients with significant macroglossia related to syndromes such as Beckwith-Wiedemann syndrome and trisomy 21; however, this procedure is avoided when possible due to the highly vascular nature of the tongue base and the potential for surgical complication. Mandibular distraction osteogenesis is a relatively invasive but highly efficacious procedure for patients with retrognathia or micrognathia, wherein the mandible is surgically fractured and affixed to an internal device that permits gradual distraction of the mandible at a rate that facilitates bone remodeling. Recent advances in this technique have permitted full internalization of a motorized distraction device in select patients, obviating the need for external pins. (36) Young infants with upper airway abnormalities may benefit from supraglottoplasty. Hypoglossal nerve stimulation is a promising intervention, currently under investigation in children, which alleviates airway obstruction due to tongue malposition by applying low-voltage electric pulses to the hypoglossal nerve in concert with diaphragmatic excursion, activating the muscles that move the tongue forward. (37) Tracheostomy is rarely indicated in the management of OSA but may be useful in patients with severe OSA associated with failure to thrive in very young infants with severe laryngomalacia, in select patients with neurologic disorders, or as a temporizing measure in patients undergoing complicated craniofacial or upper airway interventions. Treatment-emergent central apnea is a rare and generally transient complication of successful OSA therapies, particularly those surgical interventions that quickly alleviate long-standing obstruction (Table 6).

CENTRAL SLEEP APNEA

The physiology of respiratory control is complex, involving integration of multiple afferent signals from both the pons and the peripheral chemoreceptors and mechanoreceptors, at the ventral and dorsal respiratory groups and the solitary tract of the medulla, which subsequently drives respiration. (38) Children with central sleep apnea (CSA) may have some fundamental maladaptation to the transition from waking control of respiration to sleep. Central sleep apnea is a cessation or diminution of airflow due to dysregulation of the central respiratory drive. In newborns and infants, CSA is often related to immaturity or dysmaturity of the brain's control of respiration, and apnea of prematurity is a common indication for sleep consultation in the NICU. The relationship of immature control of breathing to BRUEs (brief, resolved, unexplained events, formerly "ALTE") and sudden infant death syndrome remains unclear. Apart from the relatively common idiopathic and transient causes of CSA in very young children, rare causes of CSA that must be excluded include congenital central hypoventilation syndrome (CCHS) and brainstem abnormalities such as Chiari malformation.

History and Physical Examination

A history of pauses in breathing while asleep is a frequent presenting concern for parents with young infants. Irregular breathing patterns are the rule rather than the exception in the first several months of life. (39) Specifically, periodic breathing, which is a typical neonatal respiratory pattern consisting of 5- to 10-second pauses in breathing followed by 10 to 15 seconds of compensatory tachypnea, is quite common in infancy and is a normal feature of rapid eye movement phase sleep in infants until up to 2 months after term gestational age. (20) However, when parental report of unusual breathing in an infant is complicated or otherwise not reassuringly typical for an infant, it may be difficult to distinguish true CSA from periodic breathing based purely on the history.

A PSG should be pursued in cases in which the history is notable for apnea, which is apparent to parents as being especially prolonged, or associated with any frank color change or other signs of respiratory distress. Apneas in excess of 20 seconds are typically indicative of CSA of prematurity. Similar to patients with OSA, patients with CSA may have signs or be able to report morning headache. Older patients may describe a sensation of "drowning" with arousals from CSA on awakening from sleep. A variety of syndromes, notably Rett syndrome, are associated with CSA. Patients with congenital central hypoventilation syndrome typically present in infancy and may demonstrate absence of respiratory distress despite hypoxemia and hypercapnia during cyanotic episodes.

In infants with suspected CSA, the physical examination should include an assessment of the infant's tone. In older children, the physical examination of the patient with

TABLE 6. Therapies for OSA

THERAPY	INDICATIONS
Adenotonsillectomy	Adenoidal or tonsillar hypertrophy, with strong clinical evidence of OSA or a definitive sleep study. Of note, adenoidal tissue may reaccumulate after adenotonsillectomy.
CPAP/Bi-level	PAP is the commonest noninvasive treatment for OSA, providing the additional pressure needed to help the patient overcome an upper airway obstruction.
Tracheostomy	Principally indicated in cases in which a patient is failing to thrive or has otherwise been exceptionally refractory to less-intensive OSA therapy. Tracheostomy may be helpful in cases of severe craniofacial abnormalities or neurologic issues.
Mandibular distraction	Surgical separation of the mandible is paired with an implanted mechanical distraction device, which permits the controlled separation of opposing bone at a rate that promotes bone remodeling and, thus, gradual extension of the mandible, resulting in a lengthening of the lower jaw and that yields less crowding of the tongue and associated soft tissue in the oropharynx.
Palatal expansion and distraction osteogenesis maxillary expansion	Use of these orthodontic devices expands the hard palate, correcting associated narrowing of the nasal passages.
Hypoglossal nerve stimulator	Presently in the investigational stage in children, these devices supply a titratable electric stimulus to the hypoglossal nerve while the patient is asleep, inducing the tongue to push forward and alleviate airway obstruction. This device is actuated remotely by the parents each evening at bedtime so as not to cause disruption to speech or comfort during waking hours.
Montelukast and intranasal corticosteroids	Leukotriene receptor antagonists, used principally as an adjunctive therapy to intranasal corticosteroids, likely improves nasal airflow by reducing the inflammatory bulk of the nasal turbinates and adenoidal tissue.

Bi-level=bilevel positive airway pressure, CPAP=continuous positive airway pressure, OSA=obstructive sleep apnea, PAP=positive airway pressure.

suspected CSA is targeted toward excluding actionable intracranial or brainstem abnormalities, which may be physically impinging on the centers of respiratory control in the medulla and pons. A basic fundal examination for papilledema, although potentially challenging in the pediatric patient, can be informative. The remainder of the standard sleep examination, as described in the OSA section previously herein, should be considered as warranted by the patient's presentation.

Diagnosis

PSG Findings. In children, CSA is formally defined as the reduction of airflow by 90% or more for at least 20 seconds; for 2 breath cycles if associated with an arousal, a 3% or greater decrease in arterial oxygen saturation, or a decrease in heart rate to less than 50 beats/min for at least 5 seconds; or a heart rate less than 60 beats/min for 15 seconds in infants (Table 7, Fig 3). The hallmark of CSA is that there is no respiratory effort during these events. (20) Although not standard practice, a CO_2 stimulation challenge may be useful in differentiating atypical periodic breathing or otherwise idiopathic central apneas in young infants from the intractable chemosensory dysfunction seen in CCHS. (40)

Laboratory Tests and Imaging. In infants in the first few months after birth with classical periodic breathing or brief episodes of irregular breathing pattern without abnormal neurologic examination findings, no further evaluation may be needed. Premature infants with signs of especially persistent or frequent episodes of apnea of prematurity may benefit from assessment of serum partial pressure of carbon dioxide with a blood gas test. In patients

TABLE 7. Diagnostic Criteria of Primary Central Sleep Apnea of Prematurity

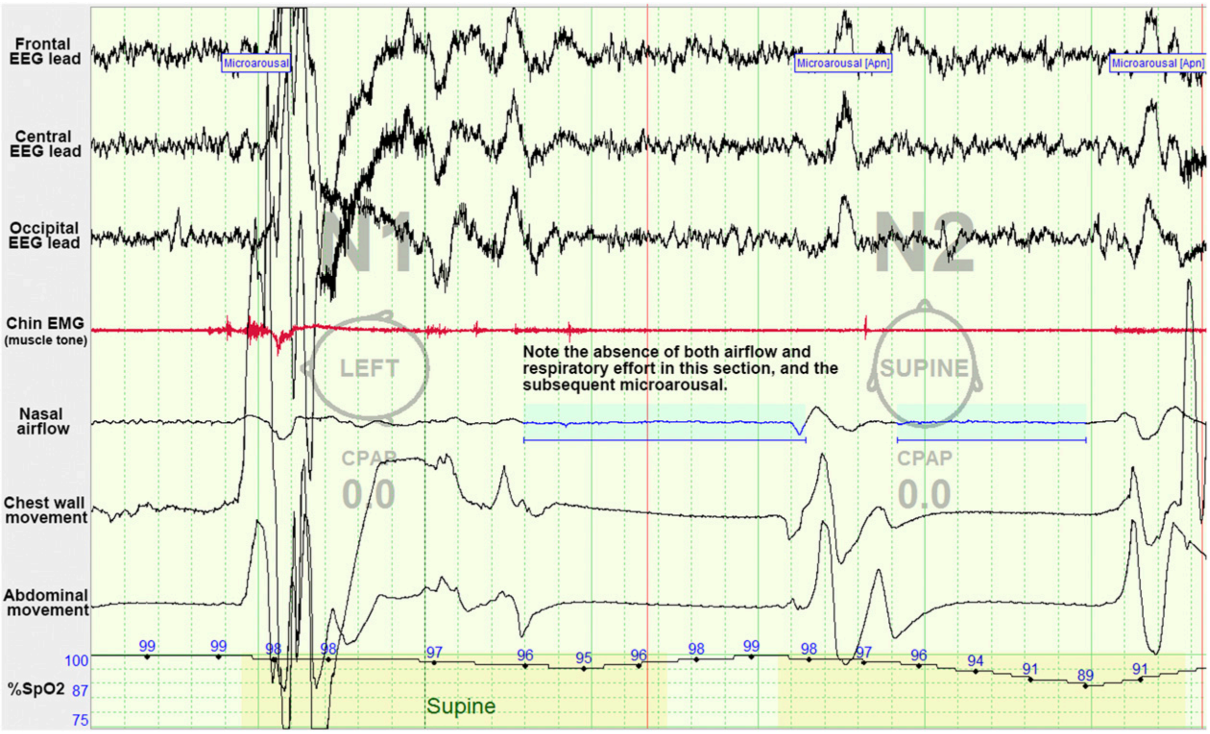
A. Apnea or cyanosis is noted by an observer, or an episode of sleep-related central apnea, desaturation, or bradycardia is detected by hospital monitoring in the postnatal period.

B. The infant has a conceptional age <37 weeks at the time of onset of symptoms.

C. Polysomnography or alternative monitoring such as a hospital or home apnea monitoring shows either:
  1. Recurrent prolonged (>20-second duration) central apneas
  2. Periodic breathing for >5% of total sleep time

D. The disorder is not better explained by another sleep disorder, medical or neurologic disorder, or medication.

Criteria A through D must be met.
Reprinted with permission from The International Classification of Sleep Disorders, *3rd ed.*



Note the absence of both airflow and respiratory effort in this section, and the subsequent microarousal.

Figure 3. Example of central sleep apnea as seen on polysomnography. In this example of central sleep apnea, there is an absence of both airflow and respiratory effort. These central events are followed by arousals. CPAP=continuous positive airway pressure, EEG=electroencephalogram, EMG=electromyography. Image courtesy of Ellen Grealish, RPSGT, R.EEG T.

with severe and refractory CSA in the neonatal period, CCHA—a syndrome of dysregulated physiologic response to hypoxemia and hypercarbia resulting in hypoventilation while asleep—should be excluded by genetic testing for *PHOX2B* mutation. In older children with CSA of unknown cause, magnetic resonance imaging of the head and neck is an important imaging modality for excluding Chiari malformation and other brainstem issues.

Management. Apnea of prematurity is often quite responsive to oral caffeine, and studies of this intervention reassuringly suggest that treated infants may experience modest neuroprotective benefits. (41)(42) Caffeine therapy is generally not indicated for idiopathic CSA of infancy that persists past 37 weeks' corrected gestational age. Patients with idiopathic CSA may benefit from the use of the carbonic anhydrase inhibitor acetazolamide, which increases respiratory drive by shifting the partial pressure of CO_2 threshold. (43)(44) Even in the absence of overt nocturnal hypoxemia, supplemental oxygen works in some patients by stabilizing or reducing the responsiveness of the peripheral chemoreceptors; however, significant sleep fragmentation often persists in patients treated with oxygen alone. (44) Patients with refractory CSA or CCHS require management with nocturnal PAP, generally Bi-level with a backup respiratory rate or an assist-control ventilator mode. Patients with evidence of Chiari I malformation, wherein the brain stem and associated center of respiratory control is compressed, benefit from urgent neurosurgical evaluation for consideration of surgical decompression.

Summary

- Based on strong research evidence and expert consensus, all children and adolescents should be screened for snoring and other signs and symptoms of sleep-disordered breathing. (3)
- Based on some research evidence as well as expert consensus, adenotonsillectomy is the first-line therapy for children and adolescents with obstructive sleep apnea in the context of adenotonsillar hypertrophy. (32)
- Based on expert consensus, in-laboratory sleep studies remain the gold standard for the diagnosis of sleep-disordered breathing in patients younger than 18 years. (21)

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1. A review of systems of a patient seen in the context of a health supervision visit is positive for snoring. Which of the following historical findings would most likely require further investigation for suggested sleep-disordered breathing?
    - A. Four-year-old child with snoring only during upper respiratory tract infections.
    - B. Six-year-old child with snoring during spring allergy season.
    - C. Six-year-old child with snoring most nights of the week and hyperactivity.
    - D. Three-year-old child with snoring 1 to 2 nights per week and pauses in breathing lasting up to 5 seconds.
    - E. Three-year-old child with snoring 1 to 2 nights per week and primary nocturnal enuresis.
2. A 10-year-old girl is seen in the clinic as a new patient. She recently was diagnosed as having obstructive sleep apnea (OSA). Her parents wish to discuss treatment options for her new diagnosis. Which of the following physical findings most likely suggests obesity-related OSA in this patient?
    - A. Acanthosis nigricans.
    - B. Ankyloglossia.
    - C. Blood pressure measurement in the 30th percentile.
    - D. BMI in the 50th percentile.
    - E. Tonsillar size of grade 1 on the Friedman tonsil scale.
3. You are evaluating a 10-year-old boy with moderate obesity, tonsillar hypertrophy, snoring, and poor school performance. Which of the following is the most appropriate diagnostic test to confirm the diagnosis of OSA in this patient?
    - A. Chest radiograph.
    - B. Electrolytes.
    - C. Home oximetry.
    - D. Polysomnography.
    - E. Pulmonary function testing.
4. An 8-year-old boy with allergic rhinitis, gastroesophageal reflux, and tonsillar hypertrophy recently underwent polysomnography, which demonstrated moderate OSA. His parents would like to avoid tonsillectomy and wish to discuss medications for sleep apnea. Which of the following is a Food and Drug Administration (FDA)–approved pharmacologic treatment for OSA in children?
    - A. Cetirizine.
    - B. Fluticasone.
    - C. Montelukast.
    - D. Omeprazole.
    - E. No medications are FDA approved for this condition.
5. An otherwise healthy 6-year-old boy underwent polysomnography due to morning headaches and observed apnea during sleep. Results show multiple prolonged episodes of central sleep apnea of greater than 20 seconds and a decrease in oxygen saturation with a nadir of 62%. His physical examination findings are normal. Which of the following is the next best diagnostic test to obtain in this patient?
    - A. Computed tomography of the brain.
    - B. Electroencephalography.
    - C. Lateral neck radiography.
    - D. Magnetic resonance imaging of head and neck.
    - E. Nasopharyngoscopy.

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Acute Myocarditis and Pericarditis in Children

Hari Tunuguntla, MD, MPH,* Aamir Jeewa, MD,† Susan W. Denfield, MD*

**Department of Pediatrics, Division of Pediatric Cardiology, Texas Children's Hospital, Baylor College of Medicine, Houston, TX*
†Department of Pediatrics, Hospital for Sick Children, Toronto, Ontario, Canada

Practice Gaps

1. The diagnoses of myocarditis and pericarditis are often delayed because they are uncommon diseases in pediatrics and because symptoms in the early stages may be overlooked in the context of current or recent viral illnesses or other systemic diseases. Early suspicion for and recognition of signs and symptoms, particularly of myocarditis, are important because the disease process can rapidly become life-threatening. Although pericarditis can also be life-threatening, it is less commonly so than myocarditis.
2. Clinicians should be aware of the predisposing factors and the clinical signs and symptoms that should increase the index of suspicion for these entities because prompt referral to the emergency department, with access to specialists with expertise in the care and support of these patients, is imperative.

Objectives After completing this article, readers should be able to:

1. Recognize the context in which myocarditis and pericarditis arise in a differential diagnosis.
2. Identify causes of myocarditis and pericarditis.
3. Recognize clinical signs and symptoms of myocarditis and pericarditis.
4. Appropriately refer patients to the emergency department for further evaluation.

INTRODUCTION

Myocardial and pericardial diseases are uncommon problems in childhood that can present as isolated diagnoses or as part of systemic diseases. Although they can have the same etiologies, and symptoms often overlap, their prognosis and treatment differ significantly. It is important to make an accurate diagnosis because clinically apparent myocarditis is much more likely to be life-threatening, and rapidly so, than pericarditis. Children with suspected myocarditis or pericarditis should be sent to an emergency department, where access to specialists with expertise in these diseases is available. The key is early suspicion for these entities to make a timely referral and diagnosis and institute appropriate therapies and interventions.

AUTHOR DISCLOSURE Drs Tunuguntla, Jeewa, and Denfield have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CMR	cardiovascular magnetic resonance imaging
DCM	dilated cardiomyopathy
ECG	electrocardiogram
EMB	endomyocardial biopsy
IVIg	intravenous immunoglobulin
MCS	mechanical circulatory support
PCR	polymerase chain reaction
PHIS	Pediatric Health Care Information System
VAD	ventricular assist device

MYOCARDITIS

Epidemiology

Myocarditis is an inflammatory disease of the myocardium due to a myriad of causes and resulting in variable degrees of myocardial dysfunction. The true incidence of myocarditis is likely underestimated because the disease can be subclinical or mild enough to go unrecognized in the context of a viral syndrome with multiple body aches and gastrointestinal and respiratory symptoms. Myocarditis is an uncommon diagnosis, accounting for 0.05% of pediatric admissions in a study using the Pediatric Health Care Information System (PHIS) database. (1) Although a small proportion of admissions, children with myocarditis were more likely to die than were children admitted with other diagnoses in that study. In a Finnish national registry study of children, the incidence of myocarditis was approximately 2 in 100,000 patient-years, with a male predominance in children older than 6 years. (2) There was no sex difference in the occurrence of myocarditis in children younger than 6 years.

In a large autopsy-based study of children (1,516 autopsies over 10 years, ages 10 days to 16 years), histologically proven myocarditis was present in approximately 2%. (3) Myocarditis accounted for 2% of infant deaths and 5% of deaths in children older than 5 years referred for autopsy. Sudden death was common, occurring in 57% in that study. When evaluated from a sudden death perspective, myocarditis accounts for approximately 5% to 6% of sudden deaths in young athletes in the United States. (4)(5) Myocarditis can also lead to the development of a chronic dilated cardiomyopathy (DCM), which is the leading cause of pediatric heart transplant in children older than 1 year. (6) Of children with a known cause for DCM, up to 46% have been reported to be due to myocarditis. (7) However, estimates of the percentage of DCMs caused by myocarditis vary, likely due to the variability in the way the diagnosis is established. Clinically it can be difficult to differentiate between a child who presents acutely in heart failure during or after an infectious illness and has an acute process due to the infection versus a child with a previously subclinical cardiomyopathy who has decompensated due to the additional metabolic stress of an infection. The gold standard for the diagnosis of myocarditis is histologic analysis on endomyocardial biopsy (EMB), but the diagnosis is often made based on other clinical studies and a compatible patient history.

Etiologies/Classification

Myocarditis can be classified based on etiology: infectious, immunologic, or toxic; histopathologically by cell infiltrate: eosinophilic, lymphocytic, granulomatous, giant cell, or neutrophilic; or by clinical features: fulminant, acute, or subacute, including chronic active with persistent inflammation or chronic persistent without persisting inflammation.(8)(9) There are multiple causes of myocarditis, many of which are shown in the Table, in conjunction with causes of pericarditis, which often overlap. Despite the many known causes, the exact etiology remains undetermined in many patients. (9)(10)(11)

Viral infection is the most commonly identified cause of myocarditis in North America and Western Europe; rheumatic carditis, *Trypanosoma cruzi* (Chagas disease), and bacterial infections such as diphtheria are common in the developing world. (9)(11)

Historically, the enteroviruses, particularly the Coxsackie group B serotypes, have been implicated as the primary viral etiology. However, more recently, viral genomes from EMBs have shown parvovirus B19, human herpesvirus 6, and adenovirus to be increasingly common. Human immunodeficiency virus has also been associated with myocarditis. Overall, there are nearly 20 known cardiotropic viruses that can result in myocarditis. (8)

Myocarditis related to bacterial infection is less common in the United States. *Borrelia burgdorferi*, which causes Lyme disease, can cause acute and chronic myocarditis, although full recovery is usually expected. In a pediatric study of 207 children with disseminated Lyme disease, 16% had carditis, and 42% with carditis had advanced heart block. (12)

Chagas disease, which is caused by the protozoa *Trypanosoma cruzi*, is commonly seen in South and Central America and is becoming increasingly recognized in the United States. A pericardial effusion is often seen during the acute phase, while DCM and left ventricular apical aneurysms can be seen in the chronic phase. Conduction abnormalities can also occur. (9)(11)

Drugs can cause myocardial inflammation by a direct toxic effect or by a hypersensitivity reaction, with the latter resulting in eosinophilic infiltrates in the myocardium. Drug-induced hypersensitivity reactions, systemic diseases such as Churg-Strauss or hypereosinophilia syndrome, and parasitic infections should be considered in the presence of peripheral eosinophilia or eosinophilic myocardial infiltration on EMB. Idiopathic giant cell myocarditis is a rare, autoimmune form of myocarditis characterized by multinucleated giant cells on histopathologic analysis. It carries a high risk of mortality unless cardiac transplant is considered. (11) However, it may recur in the transplanted heart.

Pathogenesis

The pathophysiology of myocarditis has primarily been studied in the murine mouse model. There are 3 overlapping phases: acute injury from the virus, injury related to the ensuing innate and acquired immunologic responses, and recovery, or transition to scar with DCM. (11)(13)

Acute injury often involves a viral trigger. Depending on the type of virus, different cardiac cells are affected. Parvovirus B19 (also called erythrovirus B19) and human herpesvirus 6 infect vascular endothelial cells as well as cardiomyocytes. Enteroviruses may cause a direct lytic infection of the cardiomyocyte. (11)(13)(14) Coxsackie B and adenoviruses enter the myocytes through a specific cardiac receptor called the Coxsackie and adenovirus receptor. The expression of Coxsackie and adenovirus receptor peaks in the perinatal period, which is the likely explanation for increased susceptibility in neonates, often resulting in a more fulminant presentation. Replication of the virus leads to myocyte necrosis, exposure of intracellular cardiac antigens, and activation of the host's immune system involving both cytokines and cell-mediated immunity responses. (11)(13)(14) Depending on the viral load and extent of ongoing host reaction, varying degrees of cardiac damage occur.

After the acute phase, occurring over days, a subacute phase ensues over weeks to months, mediated by the activated inflammatory cells and cytokines. In addition to attacking the virus, these responses can cause cardiac cells to lyse, inflicting further damage to the myocardium. Both T and B cells become activated which can cause an autoimmune response to cardiac cells and cell proteins. In the chronic phase there may be resolution of the infection and inflammatory response with complete recovery, or, depending on the degree of damage already inflicted, a chronic DCM may ensue. In the chronic form, the virus and the inflammatory response may or may not persist. (11)(13)(15)

Clinical Presentation

The clinical manifestations of myocarditis can range from having mild nonspecific symptoms to chest pain to cardiogenic shock. Presenting scenarios include acute heart failure of recent onset without cardiogenic shock, fulminant myocarditis with impending cardiovascular collapse, and at times malignant arrhythmias, myopericarditis resembling an acute coronary syndrome, sudden death, or an insidious onset of heart failure symptoms with chronic heart failure/DCM at presentation. (8)(15)

Children who present with heart failure symptoms in the nonfulminant form may present with shortness of breath, dyspnea with exertion, nausea, and decreased appetite, or poor feeding and tachypnea in infants, initially. These symptoms are often mistaken for other noncardiac-related illnesses or as part of a noncardiac viral syndrome. A history of a preceding infectious illness is common in many patients presenting to an office, and most infections do not result in myocarditis; therefore, it does not come up high in the differential diagnosis. During the examination it is important to note the heart rate because it often seems disproportionately elevated compared with the overall appearance of the child. By the time of presentation to the emergency department patients commonly have respiratory distress, tachycardia, lethargy, a gallop rhythm, and hepatomegaly. (16) A common mistake on abdominal examination is to palpate for the liver starting near the costal margin. It is important to start in the pelvis and palpate up from there because if the liver is very enlarged the edge will not be felt near the costal margin and may be mistaken for normal sized, or nonpalpable. Absence of rales and peripheral edema in children with heart failure is quite common, and their absence is not reassuring. When obtained, the echocardiogram demonstrates left ventricular dilation and moderate to severe systolic dysfunction with normal- to thin-appearing walls.

The fulminant form of myocarditis is more common in children than in adults, with some studies reporting an increased likelihood of recovery compared with noninflammatory DCM. (6)(17) In the fulminant form it is easier to recognize that the children are critically ill, but it is not unusual for this form to be mistaken for sepsis or severe dehydration, with large volumes of fluid given, after which pulmonary edema and cardiovascular collapse may rapidly ensue, with subsequent recognition of cardiac dysfunction. These children typically present looking very ill, with cold extremities, weak peripheral pulses, a gallop rhythm, and hepatomegaly being more common than rales and edema. Multiorgan system dysfunction or failure is common. Malignant arrhythmias may also occur. In these cases, on echocardiogram there is severely depressed left ventricular systolic function with usually a normal-sized left ventricle with relatively thick myocardium, which may be due to myocardial edema. (8)(9)(15)

Myocarditis can mimic an acute coronary syndrome. This presentation is more common in adolescents who present with symptoms of chest pain, electrocardiographic (ECG) changes suggesting ischemia, and elevated troponin levels. (15) Boys with Duchenne muscular dystrophy are particularly susceptible to myocarditis (especially enteroviral). (18) If a patient with Duchenne muscular dystrophy presents with chest pain, the clinician needs to have a high index of suspicion for myocarditis and evaluate accordingly. Differentiating between an acute myocardial infarction and myocarditis can be challenging, but myocarditis is more likely in the pediatric population. Clinicians should consider a diagnosis of acute myocarditis in younger patients without coronary risk factors, ECG abnormalities extending beyond the distribution of a single coronary artery territory, and global ventricular dysfunction on echocardiography. (8)(19) With this presentation, ventricular dysfunction tends to be mild, with most recovering completely over variable time frames.

Myocarditis can result in life-threatening arrhythmias and conduction abnormalities, including variable degrees of atrioventricular block, ventricular fibrillation/flutter, or ventricular tachycardia. Myocarditis can cause sudden cardiac death, with no symptoms until death. (8)

Myocarditis may progress to a "burned out" phase. Patients in this chronic phase typically have a more gradual progression of heart failure symptoms, and in retrospect the family recognizes that the symptoms have been building over several months. It is often difficult to differentiate chronic myocarditis from other causes of DCM. (8)

Diagnosis

After a thorough patient and family history and physical examination, the evaluation of patients with suspected myocarditis begins with biomarkers, ECG, chest radiography, and echocardiography.

Elevated cardiac biomarkers such as creatine kinase muscle-brain isoenzyme, troponin I, and troponin T confirm the diagnosis of cardiac injury. Troponin I and T levels are more frequently elevated in acute myocarditis than are creatine kinase muscle-brain levels. (11)(13)(19) Troponin T is reported to have specificity of 86% and sensitivity of 71% in children. (20) However, normal biomarker levels do not completely exclude myocarditis. The diagnostic value of viral serologies remains unclear because they may not correlate with the virus found on EMB, if performed, and serial serologies are needed. Moreover, many of the cardiotropic viruses are prevalent in the population at large and may be "innocent bystanders." (13) Viral polymerase chain reaction (PCR) of the blood or respiratory tract for common cardiotropic viruses are likely more useful than serologies, but the absence of a positive PCR does not exclude a viral cause because the viremic phase may have resolved before cardiac manifestations.

The ECG is usually abnormal. Nonspecific findings, including sinus tachycardia, ST- and T-wave abnormalities at times mimicking ischemia, and low-voltage QRS complexes, especially in the limb leads, may be seen. Figure 1 illustrates these points, with arrows pointing to the P wave and the QRS complex in lead II and the ST segment in V_5 in a patient with parvovirus myocarditis. The P wave is actually larger than the tiny QRS. The QRS complexes are barely discernable in limb leads I through aVL. The ST segments are markedly elevated in leads V_2 through V_7. Atrial or ventricular conduction delays and supraventricular or ventricular arrhythmias can occur. The presence of a Q wave or widened QRS (neither are demonstrated in Fig 1) may be associated with a worse prognosis. (9) Normal values for the QRS duration vary with age. The normal QRS duration is typically 70 to 85 milliseconds in neonates and 90 to 110 milliseconds in adolescents. (21)

Chest radiography may demonstrate cardiomegaly due to pericardial effusion or dilation of the cardiac chambers. Pulmonary edema, pulmonary venous congestion, and pleural effusions may also be seen.

There are no specific features of myocarditis on echocardiography. However, it is a valuable tool in ruling out other anatomical/structural causes of heart failure, evaluating systolic and diastolic function, cardiac chamber sizes, and wall thicknesses and identifying the presence of a pericardial effusion.

Cardiovascular magnetic resonance imaging (CMR) is becoming a routine, noninvasive tool in the assessment of myocarditis. The International Consensus Group on CMR recommends that CMR be performed in patients with a clinical suspicion for myocarditis in whom the results will affect clinical management. Although clinical management is largely supportive, some centers may use immune-modulating therapies (see the "Treatment" subsection) if their clinical suspicion for myocarditis is high. The Lake Louise criteria established the CMR criteria of myocarditis, and when 2 or more of the criteria are present it can predict myocardial inflammation with 78% accuracy. (11) Usually CMR requires general anesthesia in young children, which can pose a significant risk in a critically ill child and can limit its use, particularly because CMR findings do not usually result in a change of therapies.

Endomyocardial biopsy is considered the gold standard for the diagnosis of myocarditis. The Dallas criteria, which were published in 1987, define the histopathologic classification for myocarditis. (22) These criteria require that there is an inflammatory cellular infiltrate with myocyte necrosis not characteristic of ischemia. Borderline myocarditis is defined as the presence of an inflammatory infiltrate without myocyte necrosis on light microscopy. (13)(19)(22) The type of inflammatory cell infiltrate may guide the understanding of the etiology and therapy. The Dallas criteria are limited by their low sensitivity in part due to sampling error, as myocarditis can have a patchy infiltrate resulting in biopsy of areas that do not manifest disease. In addition, interobserver interpretation is variable. Biopsies generally lack prognostic value, except in isolated cases, such as giant cell myocarditis, which is very rare in children,

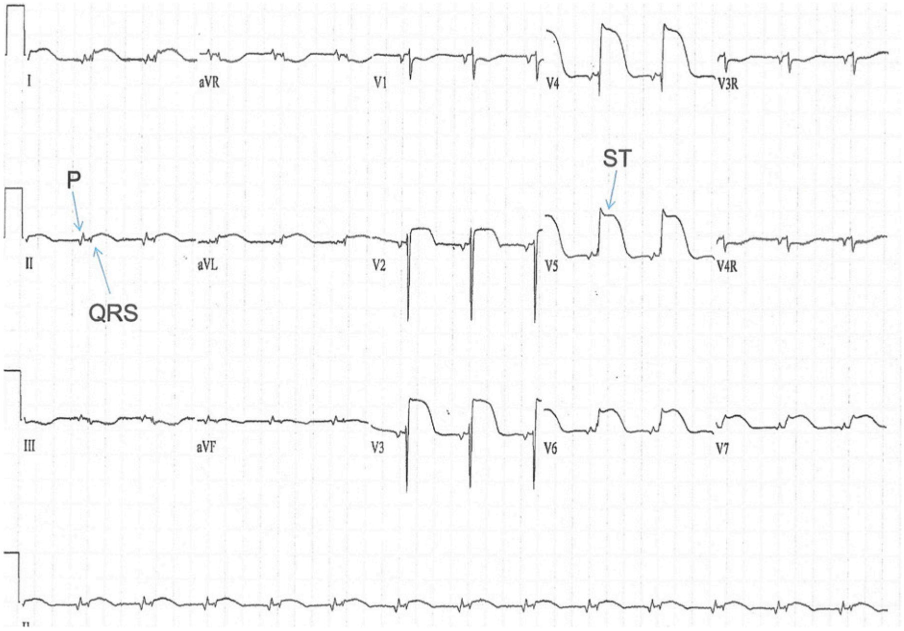

Figure 1. Electrocardiogram from a child with parvovirus myocarditis demonstrating very-low-voltage QRS complexes in leads I through aVF, V$_1$, V$_4$ through V$_7$, V$_3$R, and V$_4$R, as well as ST elevation most marked in V$_2$ through V$_7$. This appearance is called "tombstoning." The P waves are actually larger than the QRS complexes in leads I through aVF.

but has a particularly poor prognosis. More recent histologic criteria include the use of immunoperoxidase stains of cell-specific surface antigens. (8)(11)(23) A consensus statement formulated by cardiac experts in 2007 recommends that EMB be reserved for patients with fulminant or acute DCM who develop sustained or symptomatic ventricular tachycardia or high-degree heart block, who fail to respond to standard heart failure therapies, or in individuals with systemic disease known to cause left ventricular dysfunction. (24) In practice, EMB is used when it is thought to offer prognostic and therapeutic value that outweighs the potential risks. (11)(19)

Treatment

Treatment of myocarditis depends on the clinical scenario, with supportive care being the first line. Patients with fulminant or acute myocarditis often require intubation with ventilator support and usually hemodynamic support with vasopressors, inotropes, and intravenous diuretics. Patients with refractory cardiogenic shock may require mechanical circulatory support (MCS) by either extracorporeal membrane oxygenation or a ventricular assist device (VAD). Extracorporeal membrane oxygenation, which is a temporary means of MCS, may be beneficial in patients with fulminant myocarditis, as recovery in the short term is anticipated. Patients with acute myocarditis may have a more prolonged recovery and may require a VAD as a bridge to cardiac transplant or recovery. The VADs do not have a membrane oxygenator; the cardiovascular system is supported by the device, but the respiratory system is not. To be supported in this manner the patient must have an adequate respiratory status to be supported on a ventilator or be breathing spontaneously without ventilatory support. Heart failure refractory to optimal medical therapy or dependence on MCS may necessitate cardiac transplant. (11)(13)(19) The advantage of VAD support is that, depending on the device, patients can be supported for months to years and can be discharged home, even returning to school with these devices in place, while awaiting heart transplant or recovery.

Once hemodynamic stability is achieved, standard heart failure therapy, including angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, β-blockers, and spironolactone, should be implemented. Antiarrhythmic medications and placement of a temporary or permanent pacemaker may be required for tachyarrhythmias and high-grade atrioventricular block, respectively. An implantable cardioverter-defibrillator may be considered if ventricular arrhythmias persist after the acute inflammatory phase. (11)(13)

Numerous studies have investigated the use of immunosuppression in acute myocarditis with varying outcomes. The Myocarditis Treatment Trial randomized 111 adults with biopsy-proven myocarditis to receive placebo or an immunosuppressive regimen of prednisone and cyclosporine or azathioprine. (25) No difference in mortality or improvement in left ventricular ejection fraction was seen between the groups. Routine use of immunosuppressive drugs in viral or lymphocytic myocarditis is not recommended in adults; however, some centers continue to use these agents in adults and children. The use of immunosuppression can be helpful in treating myocarditis due to systemic autoimmune diseases, idiopathic giant cell myocarditis, and eosinophilic myocarditis. (13)(19)

Studies evaluating the efficacy of intravenous immunoglobulin (IVIg) also show variable results. A small case series in a pediatric population with acute myocarditis demonstrated benefit in using IVIg. (26) In a more recent retrospective pediatric study, neither IVIg nor corticosteroids individually or combined demonstrated any benefit in myocarditis. (27) In a study of adults with less than 6 months of symptoms, there was no difference in ejection fraction at 6 and 12 months between the IVIg-treated group and the control group. (28) Currently, the use of IVIg in suspected myocarditis varies between pediatric centers. (1)

If a specific viral etiology is found for which there are antiviral therapies (eg, cytomegalovirus, herpesviruses, and influenza), then specific antiviral therapy is indicated. The development of highly active antiretroviral therapy has decreased the incidence of human immunodeficiency virus–associated myocarditis. (11)

Regarding long-term treatment, oral heart failure therapies are continued as long as there is ongoing cardiac dysfunction. In the event of complete recovery the therapies may be weaned after a period of well-established normalization of function and absence of significant tachyarrhythmias. Strenuous physical activity, including physical education classes, should be avoided for at least 6 months in patients with probable or definite myocarditis. Returning to participation in competitive sports can be considered 6 months after the initial illness if the ventricular function and markers of myocardial injury, inflammation, and heart failure have normalized, and there is no evidence of clinically relevant arrhythmias on 24-hour ambulatory ECG monitoring and exercise testing. (5)

Outcome

The prognosis for individuals with myocarditis is as variable as the clinical presentation. Patients with acute myocarditis and normal cardiac function have a good prognosis overall, with a high likelihood for spontaneous recovery. Those with fulminant viral myocarditis are more likely to have recovery if adequately supported with medications or MCS during the initial phase. Giant cell myocarditis has a poor prognosis in both children and adults, with median survival of less than 6 months without cardiac transplant. (11)(13)

In a study of a multicenter cohort of 171 pediatric patients with myocarditis, 13% died or underwent cardiac transplant during their initial hospitalization. (27) In a large cohort of pediatric patients with DCM from the Pediatric Cardiomyopathy Registry, myocarditis was the most common known cause of DCM. For those with an underlying etiology of myocarditis, freedom from transplant or death at 5 years after diagnosis was 73%. (7) In contrast, 50% of those with a DCM without known myocarditis had died or undergone cardiac transplant by 5 years after diagnosis. (7)

Although progress has been made in our understanding and supportive care of children with myocarditis, ongoing efforts are required to create targeted therapies to prevent the short- and long-term consequences of this disease.

PERICARDITIS

As opposed to myocarditis that primarily affects the myocardium, pericarditis primarily affects the pericardial layers overlying the heart. The pericardium consists of 2 main layers and serves as a structural barrier to protect the heart from dissemination of infectious, inflammatory, and neoplastic diseases. (29) Typically, a small amount of serous fluid is present between the layers to provide lubrication. Irritation or inflammation of the pericardial layers, acutely or chronically, results in pericarditis.

Epidemiology

Pericarditis is the most common form of pericardial disease and has a broad range of etiologies that vary with age and geographic location (Table). (30) The true incidence of pericarditis is difficult to ascertain because asymptomatic or minimally symptomatic episodes are likely undetected, similar to mild forms of myocarditis. A large Finnish national registry study of inpatients found that of those aged 16 to 20 years, 4% of all cardiovascular admissions to hospitals were secondary to pericarditis. (31) In a US-based study of hospitalized children, using the PHIS database, of the 11,364 admissions with a diagnosis code of pericardial effusion, approximately 5% were diagnosed as having idiopathic or viral pericarditis. (32) Pericarditis was most common in adolescent males, a predilection also reported in the Finnish study. (31)

Etiologies

The common infectious etiologies of pericarditis vary geographically. In Europe and North America, viral or postviral etiologies are more common, whereas in regions where tuberculosis remains prevalent, up to 70% of cases are tuberculosis related (Table). (30) Although most viral or idiopathic pericarditis is not life-threatening, bacterial pericarditis frequently is serious and life-threatening. (31)

TABLE. **Causes of Myocarditis and/or Pericarditis in Children**

INFECTIOUS MYOCARDITIS (M) AND PERICARDITIS (P)	NONINFECTIOUS MYOCARDITIS AND PERICARDITIS
Viral	Autoimmune
• Enteroviruses such as echovirus and Coxsackie virus	• Postpericardiotomy syndrome (P)
• Influenza	• Systemic lupus erythematosus
• Epstein-Barr virus and cytomegalovirus	• Kawasaki disease
• Adenovirus	• Juvenile idiopathic arthritis (P>>M)
• Parvovirus B19	• Churg-Strauss
• Varicella	
• Mumps	Neoplastic – pericarditis
• Rubella	• Sarcomas
• Hepatitis viruses	• Lymphomas
• Human immunodeficiency virus	
• Human herpesvirus 6	Metabolic – pericarditis
Bacterial	• Uremia
• Tuberculosis	• Myxedema
• *Coxiella burnetti*	
• Pneumococcus	Trauma – pericarditis
• Meningococcus	• Radiation (may cause pancarditis)
• Staphylococci	• Direct injury includes blunt chest trauma
• Hemophilus	
• Legionella	Drug exposure/hypersensitivity reactions
• Listeria	• Tetracyclines
• Leptospira	• Sulfonamides
• *Borrelia burgdorferi* (Lyme disease)	• Penicillins
• Streptococcus	
• *Corynebacterium diptheriae*	
Fungal (important in immunocompromised hosts)	
• Histoplasma	
• Aspergillosis	
• Candida	
• Blastomycosis	
Protozoal	
• Toxoplasma	
• *Trypanosoma cruzi* (Chagas disease)	

Adapted with permission from Imazio M, Spodick DH, Brucato A, Trinchero R, Markel G, Adler Y. Diagnostic issues in the clinical management of pericarditis. Int J Clin Pract. *2010;64(10):1384–1392. Copyright © 2010 by John Wiley & Sons Inc.*

Bacterial pericarditis is more common in children younger than 2 years. (29)

Regarding noninfectious etiologies in children, there may be a higher preponderance of post–cardiac surgery–associated pericarditis compared with other systemic etiologies. (32)(33) In children who have recently undergone cardiac surgery, an effusion may develop due to an entity called *postpericardiotomy syndrome*. Additional well-described etiologies in children include rheumatologic diseases, some cancers and their associated radiation or chemotherapies, and renal failure.

Pathophysiology

When the pericardium becomes inflamed there is typically an accompanying increase in pericardial fluid, resulting in a collection large enough to be classified as a pericardial effusion. Although not common, life-threatening cardiac tamponade can occur depending on the size of the effusion and the rapidity with which it develops. This occurs because of the inability of the ventricles to fill adequately due to the pericardial fluid compressing the heart, which can culminate in cardiovascular collapse. A relatively small effusion can result in tamponade physiology if it accumulates quickly, while a very large effusion may not cause tamponade if it increases slowly. Depending on the underlying etiology of pericarditis, the fluid may be a transudate or an exudate.

However, it is also possible to have pericarditis in the absence of a significant pericardial effusion. The inflamed pericardium may also cause subjacent inflammation of the superficial myocardium, which then results in the ECG changes seen in pericarditis.

Clinical Presentation

In acute pericarditis, a history of a current or recent viral syndrome is common. The classic symptom is chest pain that is relieved in the sitting position and exacerbated when supine, coughing, or with inspiration. (29) It can be associated with fever, particularly in cases of bacterial pericarditis. The physical examination findings may be normal or may demonstrate a precordial friction rub on auscultation, which has been described as scratchy or “creaking leather” and augmented by sitting or inspiration. In cases that develop a large pericardial effusion, the heart sounds may be muffled in addition to the friction rub; however, a rub may be absent in this circumstance as well. Patients are frequently tachycardic. Neck vein distention and a decrease in peripheral pulses during inspiration, or pulsus paradoxus, may be elicited in patients with a hemodynamically significant pericardial effusion. These patients typically appear very anxious and resist lying down. However, the clinical presentation spans the spectrum from mild discomfort to the appearance of impending shock with cardiovascular collapse, the latter being less common.

Diagnosis

The initial diagnostic testing for pericarditis typically includes chest radiography; however, it is not uncommon for the cardiac silhouette and pulmonary vascular markings to be normal. In the setting of a pericardial effusion with pericarditis, the heart size may be enlarged due to the distention of the pericardial sac, often without pulmonary edema. The chest radiograph may also provide some insight into the underlying cause, such as in the case of malignancy with mediastinal involvement. The ECG changes are not always specific for pericarditis. The most common abnormality seen is diffuse ST-segment elevation in the precordial leads of the ECG without T-wave inversion in the acute phase and PR-interval depression. The ST-segment changes need to be differentiated from benign early repolarization seen in children and adolescents and myocardial infarction, which is rare in children. Similar to ECG in myocarditis, the ST-segment elevation does not follow a typical coronary distribution pattern, being more diffuse (Fig 2).

A transthoracic echocardiogram is performed to help distinguish pericarditis from myocarditis, in which there is usually cardiac dysfunction as opposed to pericarditis in which the function is normal. The echocardiogram establishes the presence and size of a pericardial effusion. Cardiac computed tomography and magnetic resonance imaging are not typically needed in acute pericarditis. These modalities may be indicated in more complicated recurrent or chronic forms, or if there is concern for constrictive pericarditis, which has a much worse prognosis and is even less common than acute pericarditis.

The laboratory findings of pericarditis are somewhat dependent on the underlying etiology. Elevations in white blood cell count, erythrocyte sedimentation rate, and other acute-phase reactants can be seen in infectious cases but may also be present in systemic autoimmune disorders and some malignancies. Troponin elevations occur in approximately one-third of patients with pericarditis, consistent with some degree of mild myocardial inflammation, which can occur subjacent to the pericardial inflammation. This often raises concern for an acute coronary syndrome, especially in conjunction with ST-segment elevation on ECG, particularly if the patient does not present to a children’s hospital. The age of the patient and the diffuse ST changes make the diagnosis of a myocardial infarction less likely

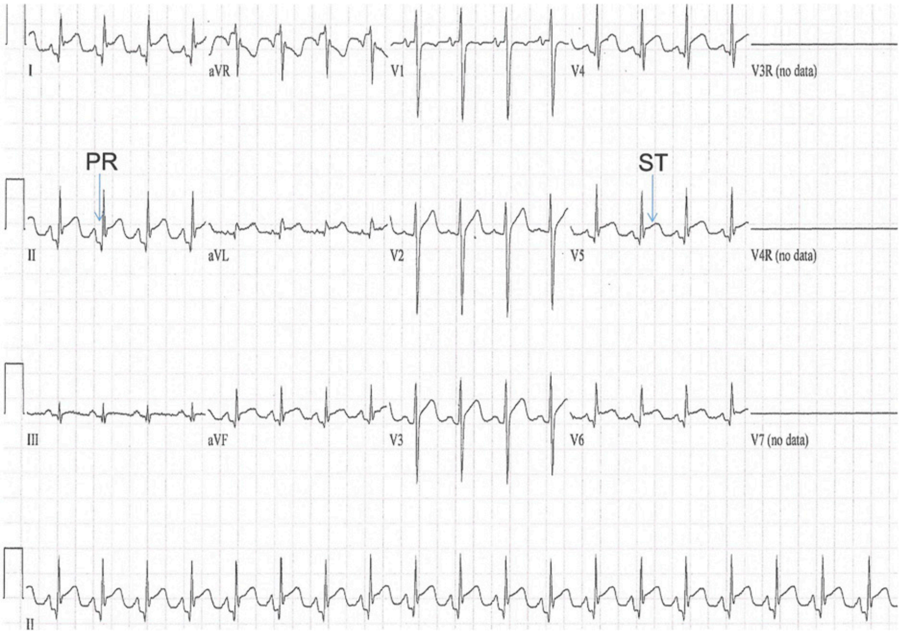

FIGURE 2. Electrocardiogram from an adolescent with pericarditis. The PR depression is most evident in leads I, II, aVF, and V_4 through V_6. The ST elevation is most prominent in leads I, II, aVL, aVF, and V_2 through V_6.

than pericarditis. Testing for infectious causes can be helpful for determining an etiology. If pericardiocentesis is performed, fluid should be sent for cultures and PCR as well as cell count, cytology, and biochemical markers.

Treatment

Nonsteroidal anti-inflammatory drugs are the basis of therapy for acute pericarditis in children. A multicenter cohort study in children with recurrent pericarditis by Imazio et al demonstrated a decrease in the recurrence of pericarditis when treated with colchicine as well. (34) Conversely, the use of corticosteroids was associated with an increased risk of recurrences in children and adults. (34)(35) In adults, guidelines recommend the initial use of a nonsteroidal anti-inflammatory drug with colchicine to reduce the recurrence risk. It is recommended that corticosteroids be avoided due to their increased risk of adverse effects and recurrences, unless there is a specific indication due to a systemic, usually autoimmune, disease that requires corticosteroid use. (35) There are novel immunomodulating therapies involving blockade of the interleukin-1 receptors (anakinra) that have been used with promising results in refractory cases of pericarditis. (36) In the setting of pericarditis with a large pericardial effusion or with signs of cardiac tamponade, pericardiocentesis can be both therapeutic and diagnostic. This procedure was performed in approximately 14% of pediatric patients with viral or idiopathic pericarditis in the PHIS database study by Shakti et al. (32) In particularly refractory cases, surgical pericardiotomy and pericardiectomy are options. Surgical pericardiotomy or pericardiectomy was performed in approximately 4% of pediatric patients in the study by Shakti et al. (32)

It is recommended that strenuous physical activities should be avoided for a minimum of 3 months after the onset of symptoms. (37) Before returning to strenuous activities, the patient should be symptom free, with normal inflammatory markers and biomarkers and normal ECG and echocardiography findings.

Outcomes

Most cases of idiopathic or viral pericarditis resolve without further sequelae. No deaths were reported in the study by Shakti et al of the PHIS database. (32) Recurrent pericarditis was reported in approximately 10% of children. The risk of death changes with the etiology, however. The risk of death is much higher in bacterial pericarditis, especially in those instances that go without treatment. (29)(31) Rarely, a constrictive form of pericarditis may develop. Constrictive pericarditis usually has an insidious presentation, typically with ascites and hepatomegaly as significant features. Unlike the acute forms of pericarditis, pericardiectomy is likely to be required and the prognosis is considerably worse. The association of pericarditis with malignancy or other systemic diseases also changes outcomes as relates to the underlying disease.

Summary

Myocarditis and pericarditis are uncommon diseases of childhood, both commonly caused by cardiotropic viruses, based on database, registry, and case series/cohort studies.(1)(2)(10)(28)(29)(30) Treatment of myocarditis is largely supportive, based on expert opinion, per a position statement by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.(10) Pericarditis typically responds well to nonsteroidal anti-inflammatory drugs and colchicine, based on adult studies and guidelines and a multicenter cohort study in children.(32)(33) Corticosteroids, unless specifically indicated for a systemic, usually autoimmune, disease, should be avoided.(32)(33) Myocarditis has a much more malignant course, with a significantly higher mortality risk than pericarditis.(7)(25)(30) Based on expert opinion, timely recognition and early referral to emergency departments with access to specialists with expertise in these diseases is necessary to maximize outcomes as much as possible.

References for this article are at http://pedsinreview.aappublications.org/content/40/1/14.

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1. A previously healthy 5-month-old girl is seen in the emergency department with a 3-day history of poor feeding and worsening decreased activity. Her parents have also noted her to be breathing faster. She has not had diarrhea or vomiting. She had a febrile illness with a rash 7 days ago that resolved after 2 to 3 days. She is toxic appearing and grunting. Her temperature is 102.2°F (39.0°C), heart rate is 186 beats/min, respiratory rate is 45 breaths/min, and oxygen saturation is 91% on room air. Cardiac examination shows no murmur, but a gallop rhythm is heard. There is evidence of subcostal and intercostal retractions, but no wheezing or rales are heard on lung examination. Her liver is 5 cm below the right costal margin. There is no peripheral edema. Creatinine kinase and troponin levels are elevated. An electrocardiogram (ECG) shows sinus tachycardia with diffuse ST elevation. An echocardiogram is most likely to show which of the following findings?
   - A. Left ventricular dilation with severe systolic dysfunction.
   - B. Normal biventricular cardiac contractility with biventricular myocardial thickening.
   - C. Right ventricular hypertrophy with normal right ventricular size.
   - D. Right ventricular dilation with right ventricular hypertrophy and normal left ventricular systolic function.
   - E. Thick myocardium and a normal-sized left ventricle.
2. A 12-year-old boy with Duchenne muscular dystrophy is hospitalized with a 2-day history of chest pain. An ECG shows diffuse ST elevation with no Q waves. Chest radiography shows cardiomegaly but no focal pulmonary infiltrates. An echocardiogram shows no pericardial effusion and moderate systolic dysfunction. Which of the following is the most likely etiology for this acute illness in this patient?
   - A. Anomalous coronary artery.
   - B. *Aspergillus fumigatus*.
   - C. Enterovirus.
   - D. Hemophilus influenza type B.
   - E. *Toxoplasma gondii*.
3. A previously healthy 3-year-old girl is seen in the emergency department with a 5-day history of increasing shortness of breath, dyspnea with exertion, and decreased appetite. She recently recovered from acute viral gastroenteritis. A chest radiograph shows normal lung fields, but cardiac size is mildly increased. Elevation of which of the following laboratory results would be most specific for the diagnosis of myocarditis?
   - A. Brain natriuretic peptide.
   - B. C-reactive protein.
   - C. Creatinine kinase.
   - D. Erythrocyte sedimentation rate.
   - E. Troponin T.

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4. A previously healthy 16-year-old boy presents to the emergency department with his parents because of a sudden onset of sharp chest pain today. He had the "flu" the past week. The pain is improved by sitting up and leaning forward. It is worse with deep inspiration. He is in mild distress. Vital signs are within normal limits. Heart sounds are normal except for a friction rub heard when sitting up. The remainder of his examination findings are normal. A chest radiograph is normal. An ECG shows ST elevation in several precordial and limb leads, particularly in those representing the left ventricle. T waves are not inverted. Troponin level is normal. Which of the following is the most appropriate next step in diagnostic testing in this patient?
   - A. Cardiac computed tomography.
   - B. Cardiac magnetic resonance imaging.
   - C. Computed tomography pulmonary angiogram.
   - D. D-dimer level.
   - E. Transthoracic echocardiogram.
5. For the same patient as in question 4, the diagnostic test performed confirmed the presence of normal cardiac function. Which of the following is the most appropriate next step in treatment?
   - A. Anakinra.
   - B. Ibuprofen.
   - C. Intravenous immunoglobulin.
   - D. Intravenous methylprednisolone.
   - E. Oral prednisone.

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Rationale for the Immunization Schedule: Why Is It the Way It Is?

Varun U. Shetty, MD,* Parul Chaudhuri, MD,† Camille Sabella, MD‡

**Department of Internal Medicine–Pediatrics †Department of Internal Medicine, Case Western Reserve University–MetroHealth Medical Center, Cleveland, OH*

‡Center for Pediatric Infectious Diseases, Cleveland Clinic Children's Hospital, Cleveland, OH

Education Gaps

1. Clinicians must understand the rationale for the current immunization schedule.
2. Clinicians must understand the basic immunologic responses associated with the various vaccine components.

Objectives

After completing this article, readers should be able to:

1. Understand the basic concepts of vaccination immunology.
2. Provide the rationale for age at first vaccine dose.
3. Provide the rationale for spacing out vaccines at 4 to 8 weeks.
4. Explain the rationale for primary series and booster combination.
5. Explain why vaccinations do not need to be started over again during catch-up.

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ABBREVIATIONS

APC	antigen-presenting cell
BCG	bacille Calmette-Guérin
CDC	Centers for Disease Control and Prevention
DC	dendritic cell
DTaP	diphtheria-tetanus-acellular pertussis
Hep B	hepatitis B
Hib	*Haemophilus influenzae* type b
IPV	inactivated polio vaccine
MMR	measles-mumps-rubella
OPV	oral polio vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PS	polysaccharide
Tfh	follicular T helper cell
VAPP	vaccine-associated paralytic poliomyelitis
WHO	World Health Organization

INTRODUCTION

Vaccines use the knowledge of the immune system to mimic infection, generate immunologic memory, and prepare the body for future infections. An ideal vaccine provides lifelong immunity from disease and protects against multiple strains of the same disease; it is safe, inexpensive, stable, and preferably not administered via injection. (1)

The main objective of the vaccination schedule is to protect individuals from disease by providing immunity before they acquire disease. (2) Long-term immunity is important in determining the effectiveness of the immunization schedule. Along with this, short-term protection, local prevalence and incidence, disease epidemiology, safety, and programmatic aspects (including number of doses, funding, organization, and cost) are important factors in determining the immunization schedule. (3)(4)

Development of vaccine schedules is based on a large body of basic sciences and epidemiologic research. There is constant review of evidence, adverse events, and epidemiology by a panel of experts.

To understand how vaccines provide protection, it is important to understand the essential components that compose the immune system and how the immune system generates a response to perceived pathogens.

OVERVIEW OF THE IMMUNE SYSTEM

The immune system can be classified into innate and adaptive immune systems (Fig 1). The innate immune system is a more primitive form of defense that includes physical, physiological, and cellular barriers. Although the innate immune system is the body's first line of defense and can act quickly, it is nonspecific. In contrast, the adaptive immune system is a sophisticated, highly specific form of defense that is capable of recognizing billions of antigens. (5)

The cellular component of innate immunity predominantly involves cells such as natural killer cells and immature dendritic cells (DCs) that attack and phagocytose foreign antigens and damaged cells of the body. (5) However, recognition of foreign/pathogenic antigens by these cells is limited to common pathogen structures that are readily recognized as non-self or dangerous. (3)(5)(6)(7) This innate response is followed by an adaptive response, with antigen-presenting cells (APCs) forming a critical link between the 2 systems. (7) The APCs specialize in processing and presenting antigens to T cells. The DCs are important examples of APCs. Components that activate APCs and the remainder of the innate immune system are similar. (7)

An immature DC undergoes activation when it encounters an antigen identified as foreign. Activated DCs experience a change in their surface homing receptors, resulting in migration to lymph nodes, where they encounter T and B cells and begin an immune reaction cascade. At this point, the adaptive immune system takes over from the innate immune system. Sometimes, the adaptive immune system can directly act on an antigen without needing an APC to present the antigen. A common example of this is the production of antibodies to polysaccharide (PS) vaccine antigens by B lymphocytes.

The adaptive system response takes more time to develop but lasts longer and produces a more robust immune response to foreign antigens. The adaptive immune system involves a targeted response to foreign antigens via T and B cells, and it interacts with the innate immune system. (3)(8) Immunologic memory (mainly B-cell memory, discussed later herein) allows rapid recognition and production of antibodies to pathogenic antigens when encountered in the future, and prevents disease. (3) This response is the major target of vaccinations. The basic tenet of vaccines is to induce effective, long-lasting immunity by triggering the adaptive immune response.

PROCESS OF GENERATION OF IMMUNITY TO VACCINE ANTIGENS

There are 2 types of responses to vaccine antigens: T-cell–dependent responses and T-cell–independent responses. The vaccine antigen is critical in determining whether the response is T-cell–dependent or T-cell–independent and, therefore, its immunogenicity (Fig 2). If the vaccine antigen is a protein antigen, such as a live attenuated virus or a protein such as hepatitis A vaccine, it will activate both B cells (that produce antibodies) and T cells. This is called a T-cell–dependent response. Polysaccharide vaccines such as 23-valent pneumococcal vaccine antigens directly trigger B cells, resulting in the production of antibodies by B cells

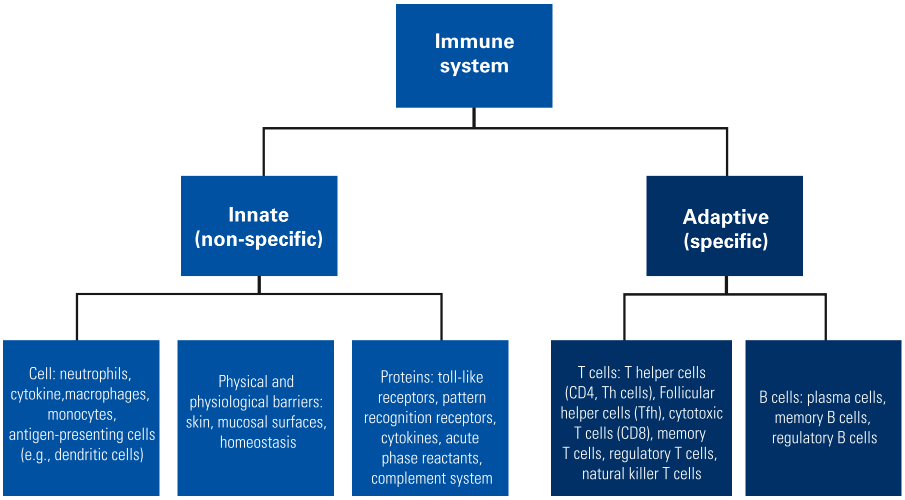
Immune system
Innate (non-specific)
Adaptive (specific)
Cell: neutrophils, cytokine,macrophages, monocytes, antigen-presenting cells (e.g., dendritic cells)
Physical and physiological barriers: skin, mucosal surfaces, homeostasis
Proteins: toll-like receptors, pattern recognition receptors, cytokines, acute phase reactants, complement system
T cells: T helper cells (CD4, Th cells), Follicular helper cells (Tfh), cytotoxic T cells (CD8), memory T cells, regulatory T cells, natural killer T cells
B cells: plasma cells, memory B cells, regulatory B cells

Figure 1. The immune system can be broadly classified into innate and adaptive, and both systems work with much interaction with each other.

without generation of immune memory. This is called a T-cell–independent response because it does not require T cells to mediate its action. Understanding the process of generation of immunity to vaccine antigens is important in understanding the vaccination schedule (Fig 3). T-cell involvement or T-cell–dependent reactions are indispensable for effective immune memory. Immune memory allows the immune system to act rapidly and specifically when the same infection is encountered in the future.

T-CELL–DEPENDENT REACTION

Live vaccines, killed vaccines, proteins, and PS conjugates generate a T-cell–dependent response. The DCs interact with the vaccine antigen when it is first delivered. The DCs are found abundantly in muscle tissue, which is why the intramuscular route is preferred during vaccination. (3) Once in contact with a foreign antigen, DCs exhibit several different receptors on their cell surfaces. These activated DCs travel to the lymph node germinal centers and activate follicular T helper cells (Tfh cells) and B cells. The B cells in the lymph nodes are not naive but have already encountered the antigen while circulating through blood. After their encounter with the antigen, they become antigen-specific and migrate to lymph nodes, where they are then ready to receive further stimuli from Tfh cells.

The Tfh cells induce massive proliferation of B cells. An initial reaction results in the production of antibodies by B

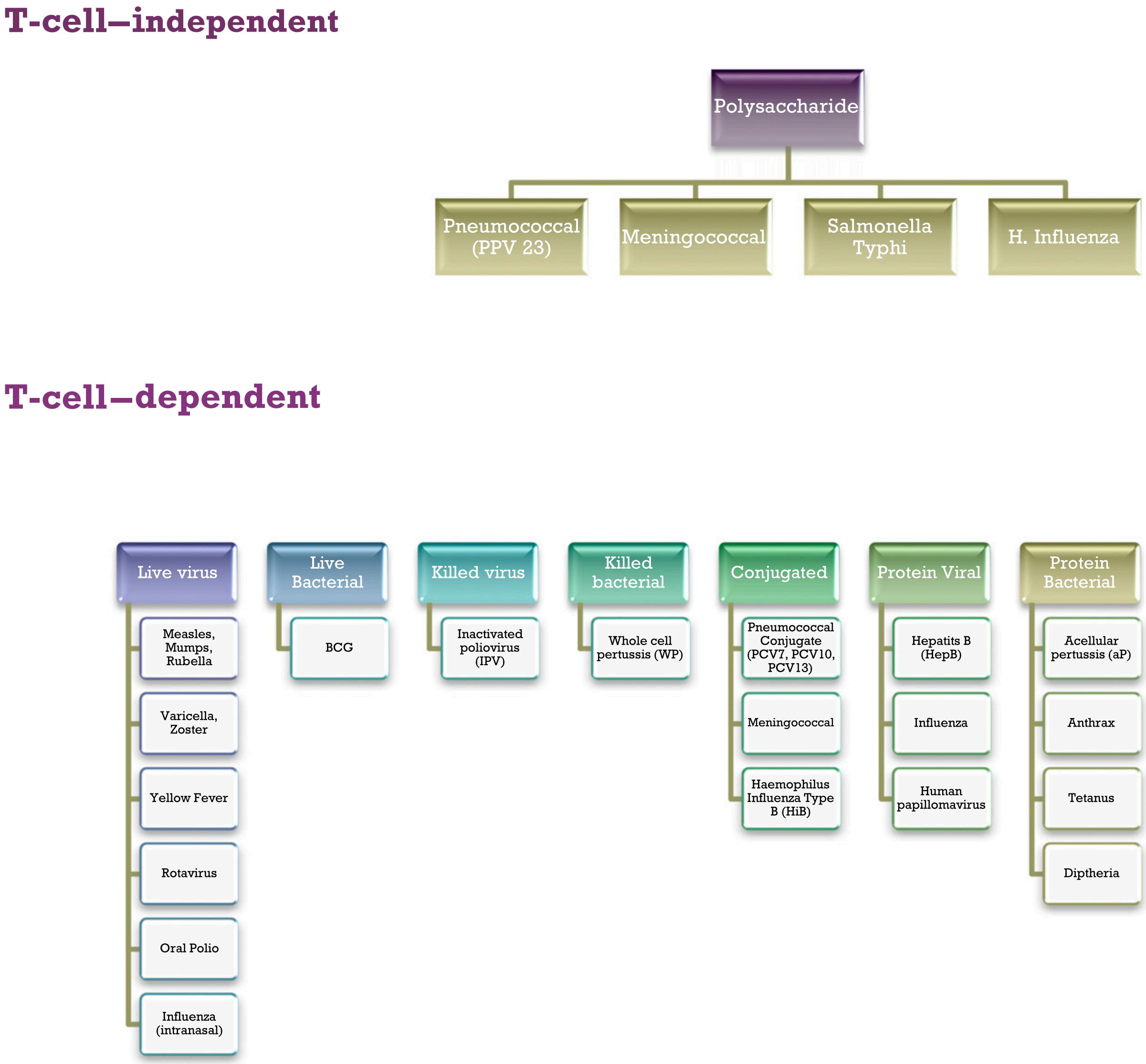

Figure 2. Vaccine antigens trigger either a T-cell–dependent response or a T-cell–independent response. T-cell–dependent responses result in immune memory, the reason why most vaccines today are live, protein, or conjugate vaccines that generate T-cell–dependent responses. Only polysaccharide antigens generate T-cell–independent responses.

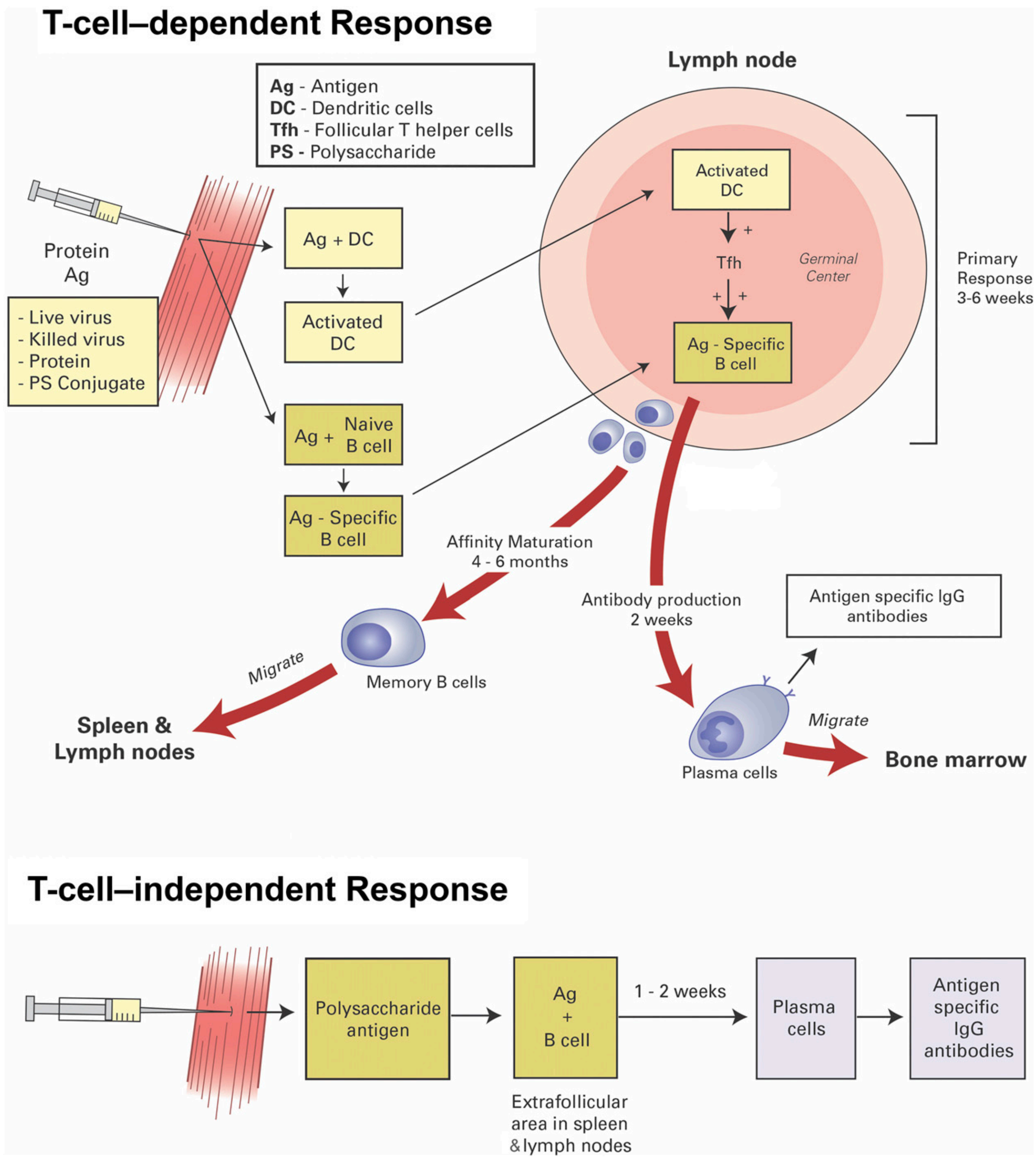

Figure 3. Overview of T-cell–dependent and T-cell–independent responses to vaccine antigen: T-cell–dependent response is triggered by protein antigens (live viruses, surface proteins, etc). The antigen activates dendritic cells and B cells, both of which travel to lymph node germinal centers. Here, activated dendritic cells stimulate follicular T helper cells, which then induce massive proliferation of B cells, which then become either memory B cells or plasma cells that produce antibodies.

cells 2 weeks after the first antigen exposure. (3)(9) A significant portion of these B cells become either plasma cells that produce antigen-specific immunoglobulin G antibodies or memory B cells that will lie dormant until faced with the exact antigen for which they were made. (3)(5)

Antigen exposure and subsequent interactions of B cells, Tfh cells, and DCs in the lymph nodes form the germinal center reaction, which is a critical part of the primary response. It takes approximately 3 to 6 weeks before the primary response self-terminates through feedback mechanisms. Doses in the priming series of vaccines are separated by a minimum of 4 weeks (usually 8 weeks or 2 months) so that they do not interfere with primary response waves in germinal centers.

After the germinal center reaction, B cells get signals from T cells and become either memory B cells or plasma cells that produce antigen-specific antibodies. The plasma cells then migrate to the bone marrow. Memory B cells take months to develop antigen specificity. For example, memory B cells generated from the measles vaccine will be active only against measles. These memory B cells do not produce antibodies. Instead, they find homes in the spleen and lymph nodes and wait until presented with an antigen, and then rapidly differentiate to plasma cells and produce antibodies specifically targeting that antigen. Over a person's lifetime there may be several billion memory B-cell types created that target specific antigens. (5) The efficient specificity that memory B cells possess results from a process called *affinity maturation* that takes approximately 4 to 6 months to develop. (3)

Memory B-cell production is important, as quantitative levels of antibodies to protein antigens wane over time. The exception to this is antibodies against live viruses; protective titers can be found decades after vaccination. (3) This may be because of the self-propagation of live viruses that results in continued stimulation of the immune system and explains the lifelong immunity to live virus vaccines such as measles vaccine after immunization.

The success of a vaccine depends on its ability to elicit a specific, robust, and long-lasting T-cell–dependent response. Most vaccines in use today are live attenuated viruses such as measles-mumps-rubella (MMR), varicella, rotavirus, and oral polio vaccine (OPV); protein antigens such as diphtheria-tetanus-acellular pertussis (DTaP) and hepatitis B (Hep B); or PS conjugates such as 13-valent pneumococcal conjugate vaccine (PCV13) and *Haemophilus influenzae* type b (Hib).

T-CELL–INDEPENDENT REACTION

Vaccines that use PS antigens elicit T-cell–independent immune responses. Most PS vaccines in use today use a carbohydrate "piece" from the bacterial cell wall. After injection into muscle, the PS antigen finds its way to B cells in the spleen and lymph nodes and triggers differentiation of B cells into plasma cells, which eventually leads to the production of poor-affinity antibodies. This takes approximately 1 week, results in the production of antibodies, is independent of signals from Th cells, and is quick to produce antibodies without generation of immune memory.

Several pure PS vaccines were used in the past. However, because of the poor immune response they generate, most PS vaccines are now conjugated with a protein or a substance that enhances immunogenicity (adjuvant). (3) When a PS is conjugated with a protein or adjuvant, it acts like a protein antigen and generates a T-cell–dependent response. Immunogenicity of pure PS vaccines before age 2 years is poor. (10) The PCV13, a PS conjugate vaccine, is recommended at 2, 4, and 6 months because it generates good immunity before age 2 years. However, the 23-valent pneumococcal PS, a pure PS vaccine against pneumococcus, is given only after 2 years of age. A pure PS vaccine is suitable when rapid induction of immunity is required; for example, a traveler wanting temporary but rapid immunity from *Salmonella typhi* when visiting an endemic region.

RATIONALE FOR THE IMMUNIZATION SCHEDULE

The underlying goal of the immunization schedule is to achieve effective, lasting immunity against diseases. This means inducing lasting immunologic memory and production of persistent antibodies. Although a prerequisite for understanding the rationale for the immunization schedule, learning the immune response to a vaccine antigen is not sufficient by itself. One needs to know local epidemiologic patterns of disease to optimize the timing of priming and booster doses. Programmatic considerations, such as grouping of vaccines, cold chain storage, number of doses, and interference by competing antigens in generating immune responses, all play roles in developing a vaccination schedule.

We will consider dosing regimens of some important vaccines used in the regimen and explain why they are dosed in their current form.

Age at First Dose and the 2-, 4-, 6-month Schedule

Priming doses are required to generate immune memory. These are the initial doses that generate a germinal center reaction and result in production of memory B cells and plasma cells that produce antibodies.

In the United States, priming doses of DTaP, Hib, rotavirus, PCV13, and inactivated polio vaccine (IPV) are all given at 2, 4, and 6 months, although some formulations of Hib and rotavirus are given at 2 and 4 months. Infants younger than 1 year have the greatest risk of mortality from pertussis, and mortality from diphtheria is highest in those younger than 10 years. (11)(12) Similarly, the prevalence of bacterial meningitis before the widespread use of Hib and pneumococcal conjugate vaccines was the highest in the first year of life. Therefore, protection against these infections throughout the first year of life is essential.

Immunization before 6 weeks of age for most antigens results in a weaker response and poorer immune persistence, mainly because of the immaturity of the immune system. (3)(13) The *magnitude* of an antibody response, ie, antibody titers, is higher with increasing age at first dose. (13) However, the 6-, 10-, 14-week schedule along with the addition of a booster dose generates equivalent immune memory compared with schedules that start at or after 2 months of age and is more appropriate depending on local epidemiology of disease. (14)(15)(16) Thus, the recommended age to give most vaccines is at 2 months in the United States, at 3 months in some European countries, and at 6 weeks where the burden of disease is high. (13)(17)(18) Hepatitis B, bacille Calmette-Guérin (BCG), and OPV are exceptions to this; they are all given at birth and are discussed in more detail later in this article.

A minimum of 3 weeks between primary doses prevents interference of primary waves of immune response. (3) This is because a primary response self-terminates in 3 to 6 weeks. Vaccines are spaced out at 4- to 8-week intervals to avoid competing immune responses between primary waves of germinal center reaction. Several studies have examined different priming schedules (eg, a 3- and 5-month 2-dose schedule, as well as 2-, 4-, 6-month and 2-, 3-, 4-month schedules), and these studies suggest that all schedules generate immune memory. (13)

The longer the interval between doses, and the older the infant, the longer the persistence of response to the vaccine. (3) Closely spaced vaccine doses (1–2 weeks) would give protection sooner, which is useful when rapid induction of immunity is required. (3) But this immune response would not be as long-lasting as when the doses are spaced out at 4 to 8 weeks. Vaccine schedules try to achieve a balance between early protection and best immune response by spacing out vaccines enough to allow immune maturity but early enough to protect before acquisition of disease.

The World Health Organization (WHO) Expanded Program on Immunization schedule recommends beginning diphtheria-tetanus-pertussis whole cell or DTaP vaccine as early as 6 weeks, and providing 3 priming doses at least 4 weeks apart, with the first booster dose between 12 and 23 months. (17) This is used by many developing countries where the incidence and prevalence of diphtheria and pertussis are higher than in industrialized nations. Starting at 6 weeks provides very early immunity, but the immune system is not as mature as it would be if started at 2 months. However, studies have shown that the 6-, 10-, 14-week schedule provides good immune response and that the addition of a booster dose generates equivalent immune memory compared with schedules that start at or after 2 months of age and is more appropriate for local epidemiology of disease. (13)(19)

Regimens in different countries are based on principles of vaccination immunology and differ according to local epidemiology and programmatic preferences (Table 1).

Table 2 lists priming dose regimens for diphtheria-tetanus-pertussis vaccine in various countries. Although this list is not exhaustive, it demonstrates the use of knowledge of vaccination immunology and local epidemiology to develop a vaccine regimen. Note that the doses are separated by a minimum of 4 weeks in all recommended schedules to prevent interference in primary waves of immune response.

Prime-Boost Schedule

As reviewed previously herein, affinity maturation is the process by which memory B cells complete the process of developing antigen specificity. This process takes approximately 4 to 6 months. Antibodies generated in the initial wave of primary response during priming doses eventually wane over a period of months.

Allowing at least a 6-month gap between the last primary dose and the first booster dose allows completion of the affinity maturation process and development of highly specific memory B cells. The longer the gap between the primary and booster doses, the better the immune persistence. (3)

TABLE 1. Factors Influencing the Vaccination Schedule (4)

Vaccination immunology:
• Immune maturity, maternal antibodies, magnitude of immune response, and immune memory are important considerations in determining vaccination schedules
Local epidemiology:
• Ideally, the dose of vaccine should precede the earliest, most susceptible age at acquisition of disease
• High incidence and prevalence generally favors earlier immunization
• Eradication of disease/infection could lead to elimination of use of certain vaccines, eg, small pox vaccine
Programmatic considerations:
• Organization of vaccination drives, educating local practitioners
• Availability of combined vaccines
• Cost (eg, acellular pertussis is more expensive than whole cell pertussis), maintaining cold storage, and heat stability are some important factors influencing the inclusion and timing of vaccines in the schedule

TABLE 2. Comparison of Diphtheria-Tetanus-Pertussis Priming Dose Regimens

COUNTRY	PRIMING DOSE REGIMEN
United States	2 mo (8 wk), 4 mos (16 wk), 6 mo (24 wk)
United Kingdom	2 mo (8 weeks), 3 mo (12 wk), 4 months (16 wk) (13)
Italy	3 mo (12 wk), 5–6 mo (20–24 wk) (13)
World Health Organization Expanded Program on Immunization	Begin at 6 wk, 4-wk minimum interval between doses, 3 priming doses in total

A booster dose stimulates immune memory and triggers memory B cells to become plasma cells and generate antibodies. These antibodies persist in the blood for several months, even years, and neutralize antigens produced by pathogenic microbial agents before they have an opportunity to cause disease.

Spreading out vaccine doses for better immune memory needs to be balanced with providing effective protection before an exposed child develops disease. Therefore, local epidemiology must be taken into consideration when determining vaccine timing.

All schedules recommend booster dose administration at least 6 months after the last priming dose. (2)(17) Most schedules space out booster doses further from priming doses because longer intervals between doses result in longer immune memory. For example, in the United States, the DTaP booster is given 9 months after the last priming dose and the Hib booster is given at least 6 months after the last priming dose. (18) The WHO Expanded Program on Immunization schedule also recommends pertussis booster at 1 to 6 years of age, although it states that the booster dose must be separated by at least 6 months. (17) The Centers for Disease Control and Prevention (CDC) also recommends spacing out the booster dose by at least 6 months in the case of delayed immunizations. (18) This is to allow for earlier protection without compromising on immune memory.

In summary, booster doses allow for maintenance of sustained antibody levels and should be given at least 6 months after the last priming dose to allow for affinity maturation.

MMR and Varicella Vaccines

The MMR and varicella vaccines are examples of how giving a live virus vaccine generates longer immunologic memory. Although live virus, killed virus (eg, IPV), protein (eg, tetanus toxoid), and PS conjugate (eg, Hib, PCV13) vaccines all elicit T-cell–dependent responses, generate immunologic memory, and offer effective, long-lasting protection, live vaccines always generate the most powerful immune responses. This is because the amount of antigen exposure results in multiple primary responses all over the body, as well as persistent exposure to the pathogen that generates more powerful antibody responses. Live virus vaccine is also the only type of vaccine that generates a CD8 response, which results in direct killing of infected cells and indirect destruction of cells via cytokines. (3) Live vaccines generate lifelong immunity not only because they generate the T-cell–dependent response that generates immune memory but also because the virus multiplies and persists in the body, thus constantly exposing the host to the antigen and stimulating the immune system. This results in survival of plasma cells in bone marrow for long periods, which generate antibodies for decades. Only live vaccines generate an antibody response that is detectable for decades, even in the absence of subsequent antigen exposure.

The MMR and varicella vaccines are given only after 6 months of age (preferably after 12 months). This is to avoid neutralization by maternal antibodies and a poor immune response from an immature immune system. Presence of maternal antibodies plays an important role in the ability of the MMR vaccine to generate immunogenicity. These antibodies usually disappear between 6 and 9 months of age. They interfere in replication of the live attenuated measles virus, thereby preventing the development of multiple foci of primary reaction. Maternal antibodies to measles significantly reduce immune response and can affect vaccine efficacy. In addition, studies have demonstrated that infants younger than 6 months of age do not mount a good immune response to the MMR vaccine, even in the absence of maternal antibodies. (20)

Multiple studies have shown the effect of maternal antibodies on the efficacy of the MMR vaccine: 98% of children developed protective antibodies to measles if vaccinated after 12 months of age, (20) and almost all children developed protective antibodies to measles with a first vaccine dose at 6 months and a second dose at 12 months or a first dose at 15 to 17 months and a second at 4 to 6 years. (20) A second dose is given to protect the minority of children (~5%) who do not develop protective antibodies with the first dose. A booster dose, therefore, is not required for MMR vaccine in childhood.

The CDC and the American Academy of Pediatrics, therefore, recommend administration of MMR and varicella vaccines at 12 months of age, with a second dose at 4 to 6 years. However, if the child is traveling to a measles-endemic area, MMR vaccine can be given as early as 6 months of age. In such cases, revaccinating at 12 to 15 months and giving a third dose at least 4 weeks later are required.

Vaccines at Birth

In the United States, only the Hep B vaccine is given at birth. Studies have shown that in children with birthweight of more than 2,000 g, a dose of Hep B at birth with subsequent doses at 1 to 2 months and 6 to 12 months demonstrated an excellent immune response. (21) Before the routine use of Hep B vaccines, 30% to 40% of children with chronic Hep B acquired the disease via perinatal or early childhood transmission. (22) Moreover, almost half of all new mothers who are positive for Hep B surface antigen are not identified. (22) This underscores the need to protect infants and children when they are most vulnerable. Although preterm infants weighing less than 2,000 g do not have good immune responses with a birth dose of Hep B vaccine, all premature infants, irrespective of gestational age or birthweight, are protected with the 3-dose Hep B vaccine series started at 1 month of chronological age. (21) Therefore, the CDC recommends that all infants weighing more than 2,000 g must get the first dose of Hep B within 24 hours of birth and preterm infants weighing less than 2,000 g at birth must get the first dose at 1 month of age. (23)

Vaccines given at birth in other countries include OPV and BCG. The OPV has been shown to generate good gut immunity when given at birth even in the presence of maternal antibodies. (24) It is safe and provides the earliest protection to infants from polio. (24)(25) It is indispensable in areas where poliomyelitis is endemic, such as Nigeria, Afghanistan, and Pakistan, or where there is risk of importation of disease from neighboring countries. (26) However, OPV is associated with rare adverse effects of vaccine-associated paralytic poliomyelitis (VAPP) and vaccine-derived polioviruses. The incidence of VAPP was higher in industrialized countries with the first dose of OPV, most likely due to higher immunogenicity of vaccine antigen compared with low- to middle-income countries. The reason for this is not understood well, but a higher prevalence of maternal antibodies in low-income settings, and competing infections might be contributing factors. (27)(28) Therefore, although OPV has been very effective in eradication of polio, it is not necessary in countries that have already achieved poliomyelitis eradication, have low risk of polio importation and transmission, and continue to have good rates of immunization. The IPV does not cause VAPP. It is recommended that an IPV-only schedule may be considered in such countries, including the United States. (27)

The CDC does not recommend routine BCG vaccine to children born in the United States because the general risk of transmission of tuberculosis is low. (29) The WHO does acknowledge the limited efficacy of BCG in that it does not protect from primary infection or reactivation of latent tuberculosis, a major source of tuberculosis infection in the community. (30) However, BCG vaccine does protect children from miliary tuberculosis and tuberculous meningitis in the first 5 years of life. (25) The BCG vaccine also is safe, which is why it continues to be recommended at birth in regions where risk of tuberculosis transmission remains high. (25) The OPV and BCG vaccines are good examples of how local epidemiology of disease influences timing as well as type of vaccines included in vaccination schedules.

Catch-up Vaccines

It is not recommended that the immunization schedule be started again in patients with delayed immunization. This is due to the generation of immune memory. Although antibody titers wane with time, memory B cells in the spleen and lymph nodes readily recognize the antigen with subsequent exposures to vaccine antigens and produce antibodies. A long time between priming doses induces better immunologic memory. However, because of the long time between doses, children with delayed vaccines are susceptible to serious vaccine-preventable infections. Therefore, the CDC catch-up schedule recommends a minimum of 4 weeks between catch-up doses of vaccines and that the vaccination schedule does not have to be started all over again. (18)

The same CDC catch-up schedule can be applied to children who have no immunizations until a later stage. Because the primary reaction in lymph nodes lasts 3 to 6 weeks, an accelerated schedule with priming doses separated by a minimum of 4 weeks can be used. However, age at the start of vaccines, epidemiology, and national immunization schedule recommendations should be considered when deciding on the optimal vaccine schedule for such children.

VACCINE EXEMPTIONS AND DELAYS

There is strong evidence that skipping vaccine doses increases the risk of acquiring vaccine-preventable diseases such as measles and pertussis. (31)(32) According to the American Academy of Pediatrics, “There is no ‘alternative’ immunization schedule. Delaying vaccines only leaves a child at risk of disease for a longer period of time; it does not make vaccinating safer.” (33) It is best to adhere to recommended schedules and discourage alternate, unvalidated schedules.

CONCLUSION

Development of vaccine schedules is based on a large body of basic sciences and epidemiologic research. There is constant review of evidence, adverse events, and epidemiology by panels of experts. The immunization schedule is updated accordingly. It is critical that we understand the basis of the vaccination schedule so that we can better educate ourselves and our patients, and use available evidence to best protect them.

Summary

- Based on consensus, the main objective of vaccines is to provide protection against vaccine-preventable diseases by providing effective short- and long-term immunity from disease. (4)
- Based on strong evidence, there are 2 types of responses to vaccine antigens: T-cell–dependent and T-cell–independent responses. The T-cell–dependent response is critical in generating effective immunologic memory. (3)
- Based on strong evidence, T-cell–independent response is triggered by polysaccharide (PS) vaccine antigens. PS antigens trigger B cells to differentiate into plasma cells that produce antigen-specific antibodies that are short-lived. There is no generation of immune memory in this type of response.
- Most vaccines are developed with the goal of triggering a T-cell–dependent response.
- Based on strong evidence, vaccine antigen type is crucial in determining whether the generated response will be T-cell–-dependent or T-cell–-independent. Live virus, protein, and polysaccharide conjugate vaccines all generate T-cell–dependent responses. (3)(5)
- Based on strong evidence, immune response and memory are both better with administering vaccines after 2 months of age. (13)
- Based on strong evidence, vaccines can be started at 6 weeks of age if the risk of contracting disease is high, provided all 3 priming doses and booster doses are appropriately given thereafter. (13)(17)
- Based on strong evidence, immune memory generation allows us to continue vaccine schedules rather than start over in children with delayed vaccinations. (3)
- Based on strong evidence, vaccine exemption increases the risk of acquiring vaccine-preventable diseases. (31)(32)
- The immunization schedule is based on the guiding principles of vaccination immunology, local disease epidemiology, and programmatic needs, which ultimately result in an effective and pragmatic vaccination schedule.

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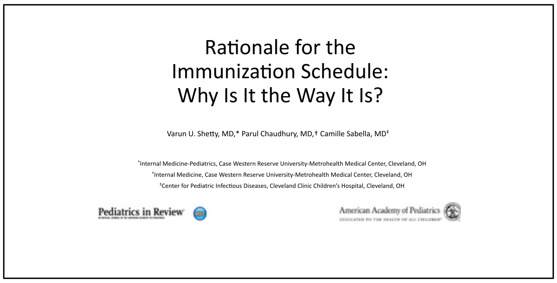
Rationale for the
Immunization Schedule:
Why Is It the Way It Is?

Varun U. Shetty, MD,* Parul Chaudhury, MD,† Camille Sabella, MD‡

*Internal Medicine-Pediatrics, Case Western Reserve University-Metrohealth Medical Center, Cleveland, OH
†Internal Medicine, Case Western Reserve University-Metrohealth Medical Center, Cleveland, OH
‡Center for Pediatric Infectious Diseases, Cleveland Clinic Children's Hospital, Cleveland, OH

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1. While reviewing your daily schedule you note that a patient is scheduled to return for vaccines just 2 weeks after the previous dose. You ask your nurse to reschedule the patient and explain that the minimum interval between doses of all vaccines is at least 4 weeks. Which of the following best describes the reason a minimum of 4 weeks is required between vaccine doses?
   A. Antigen-presenting cells of the innate immune system require approximately 4 weeks to attack vaccine antigens.
   B. Antigen-presenting cells of the innate immune system require approximately 4 weeks to travel to muscle.
   C. Interference between successive waves of priming responses in the lymph nodes is avoided by minimum spacing of 4 weeks.
   D. Memory B cells need approximately 4 weeks to develop antigen specificity.
   E. Memory B cells need approximately 4 weeks to migrate to the spleen and lymph nodes.
2. A patient is seen in the clinic for a 6-month health supervision visit. After receiving the required immunizations, the clinician provided the mother with anticipatory guidance and instructed her that the baby will be due for a health supervision visit at 9 months of age, at which time he does not need any vaccines. Booster vaccines will be provided at the 12- and 15-month health supervision visits. The nurse informs the clinician that at checkout the mother is inquiring whether the diphtheria-tetanus-acellular pertussis (DTaP) #4 can be given at the 9-month health supervision visit to space out the vaccines. The clinician explains to the nurse that the interval between DTaP #3 and DTaP #4 must be at least 6 months. Which of the following is the most appropriate explanation for the rationale of this recommendation?
   A. A shorter interval between the primary series and booster dose will result in a severe local reaction at the injection site.
   B. A shorter interval between the primary series and booster dose will result in a strong immune reaction.
   C. A shorter interval between the primary series and booster dose will increase immune persistence.
   D. A 6-month interval before the booster dose allows the development of highly specific memory B cells for longer immune memory.
   E. A 6-month interval before the booster dose is necessary to generate the T-cell–independent antibody response.
3. The mother of a 6-month-old boy brings him to the clinic because the family will be traveling internationally next month and will be abroad for 8 weeks. Which of the following is the best plan for immunizing this patient?
   A. Give measles immune globulin now.
   B. Give measles immune globulin 1 week before travel.
   C. Give measles-mumps-rubella (MMR) #1 now and MMR #2 at 4 to 6 years of age.
   D. Give MMR #1 now and MMR #2 at 12 to 15 months of age.
   E. Give MMR #1 now, MMR #2 at 12 to 15 months, and MMR #3 at least 4 weeks later.

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4. While reviewing the records of a new patient from Africa, you note that he received his first dose of oral polio vaccine (OPV) at birth. Which of the following best explains the approach to immunization of newborns?

    A. Newborns in other countries may appropriately receive OPV and/or bacille Calmette-Guérin (BCG) vaccines based on the local epidemiology of disease.
    B. Newborns should not receive any vaccines other than hepatitis B due to the immaturity of their immune system.
    C. Newborns should not receive any vaccines other than hepatitis B due to interference by maternal antibodies.
    D. Newborns should not receive BCG due to risk of dangerous adverse effects.
    E. Newborns should routinely receive hepatitis B vaccine at birth only if the mother is known to be hepatitis B surface antigen positive.

5. A 4-year-old boy has returned to your practice after living in Haiti for several years. His mother reports that he had no medical care during that time. Your records indicate that he received his 2- and 4-month vaccines only before leaving the United States. Which of the following describes the most appropriate approach to further immunization of this child?

    A. Further immunization should be deferred until the next visit to determine whether the parent can obtain documentation of additional vaccines.
    B. Some immunizations should be deferred to avoid overwhelming the immune system with too many antigens.
    C. The vaccine schedule should be restarted because the interruption in the schedule is too long.
    D. The vaccine schedule should be restarted because the priming series is incomplete.
    E. The vaccine schedule should be resumed today, giving all age-appropriate and catch-up vaccines without repeating any previous doses.

Rationale for the Immunization Schedule: Why Is It the Way It Is?

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Index of Suspicion

1

Syncope in a 16-year-old Girl

Arhanti Sadanand, MD,* Meagan Ladell, MD,* Kayleigh Fischer, MD†

*Department of Pediatrics and †Department of Pediatrics, Division of Pediatric Emergency Medicine,
St Louis Children's Hospital/Washington University in St Louis, St Louis, MO

PRESENTATION

A previously healthy 16-year-old girl is transferred from a referring facility for syncope and altered mental status. The previous day, she received the meningococcal vaccine. After a stressful conversation with her father, she began to complain of chest pain, diaphoresis, and nausea. She vomited, became clammy, and fell to the ground unresponsive. She was brought to the referring facility, where she was given epinephrine, diphenhydramine, methylprednisolone, famotidine, and 4 L of isotonic fluids for a possible anaphylactic reaction to the vaccine. She remained groggy, tachycardic, and anuric.

After transfer, her vital signs are as follows: temperature, 97.5°F (36.4°C); heart rate, 120 beats/min; respiratory rate, 23 breaths/min; blood pressure, 95/44 mm Hg; and oxygen saturation, 98% on room air. On physical examination, she is sleepy but responsive, with a Glasgow Coma Scale score of 15, delayed capillary refill, 2+ pulses, and hepatomegaly to 4 cm below the costal margin. The remainder of her examination findings are within normal limits.

She denies pain, fevers, night sweats, unintended weight loss, exercise intolerance, or peripheral edema. She reports a similar episode during final exams during her previous school semester that was attributed to stress after a reassuring evaluation. She was started on an antidepressant medication, which she discontinued taking 3 weeks ago due to improvement in symptoms.

Initial laboratory results show metabolic acidosis with venous pH 7.29; carbon dioxide level, 38 mEq/L (38 mmol/L); white blood cell count, 28,800/μL (28.8×10^9/L); lactate level, 40.5 mg/dL (4.5 mmol/L); blood glucose level, 187 mg/dL (10.4 mmol/L); troponin I level, 0.04 ng/mL (0.04 μg/L); brain-type natriuretic peptide level, 42 pg/mL (42 ng/L); and cortisol level, 49 μg/dL (1,352 nmol/L). Chest radiography shows diffuse nodular opacities throughout both lungs (Fig 1). An electrocardiogram is performed that shows right axis deviation and pericardial inflammation (Fig 2).

She is hospitalized in the ICU due to hypotension and tachycardia and is initiated on a vasopressor drip to maintain blood pressures. An echocardiogram leads to the cause of her syncope.

EDITOR'S NOTE
We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Sadanand, Ladell, and Fischer have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

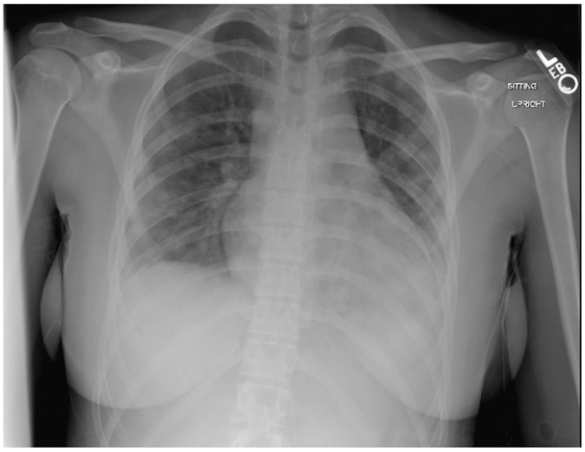

Figure 1. Patient's chest radiograph.

DISCUSSION

Differential Diagnosis

Our initial differential diagnoses included infectious myocarditis, dilated cardiomyopathy, bacterial sepsis, pulmonary embolism, ingestion, atrial myxoma, lymphoma, tuberculosis, hemophagocytic lymphohistiocytosis, human immunodeficiency virus, and fungal pneumonia.

Actual Diagnosis

Echocardiography showed a right atrial mass extending into the superior vena cava and a large pericardial effusion with tamponade physiology. A chest computed tomographic (CT) scan showed a mass centered in the epicardium of the right atrial wall involving the pericardium and extending through the myocardium to fill the right atrium (Figs 3 and 4). It also showed a small right pleural effusion, a heterogeneous appearance of the liver, small-volume ascites, and numerous small masses in the lung fields. The right atrial mass was biopsied, and a sample was sent to the pathology laboratory. Microscopic features, immunohistochemistry panel results, and clinical location of the mass in the right atrium were most consistent with a primary cardiac angiosarcoma with pulmonary metastases.

The Condition

A recent population study found the incidence rate of primary cardiac tumors to be 1.38 per 100,000 persons per year. (1) A pediatric review at 1 center found that approximately 95% of primary cardiac tumors were benign and 5% were malignant. (2) Of these malignant tumors, primary sarcomas are more common than primary lymphomas, and cardiac angiosarcomas are the most common of the cardiac sarcomas. There is a male:female predominance of approximately 2:1 to 3:1. (3) Risk factors for angiosarcomas include previous irradiation, chronic lymphedema, exogenous toxins, and familial syndromes, including NF-1, BRCA1, BRCA2, Maffucci syndrome, and Klippel-Trenaunay syndrome. (4)

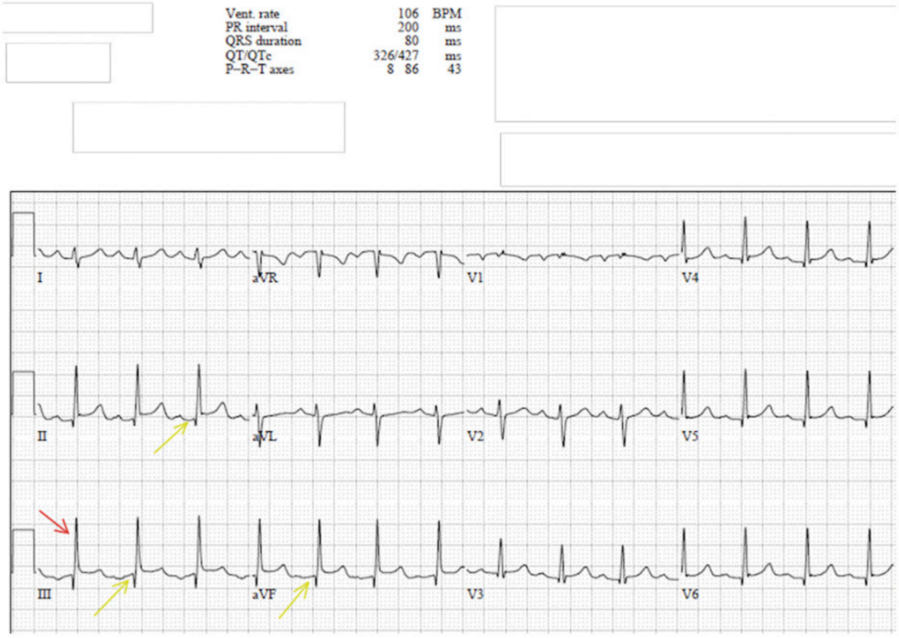

Figure 2. Patient's electrocardiogram; yellow arrows indicate PR depression showing pericardial inflammation/pericarditis, and red arrow shows right axis deviation concerning for right heart strain.

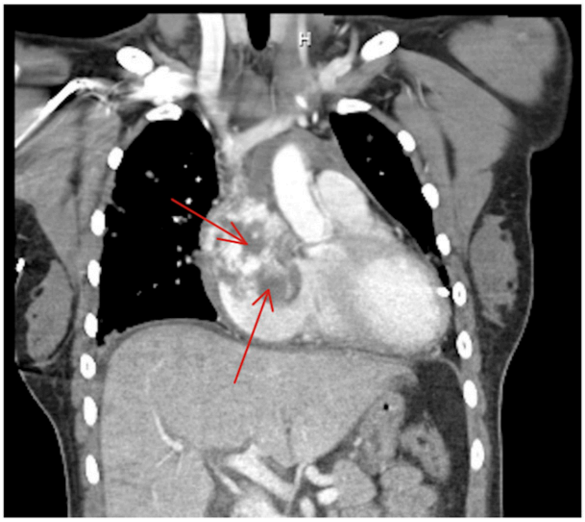

Figure 3. Patient's chest computed tomographic scan, coronal view; red arrows indicate the primary tumor.

Cardiac angiosarcomas arise from the endothelial lining of blood vessels or the lymphatic system and tend to occur in the right atrium. (3)(5) Unlike most sarcomas, they are more likely to metastasize to the liver and lungs. Unfortunately, many cardiac angiosarcomas present with these systemic metastases, which decreases the median chance of survival. (6) Treatment is generally composed of resection if possible, and chemotherapy with adjuvant radiotherapy. Cardiac angiosarcomas have low median survival times ranging from 6 to 24 months. (7) Some centers have performed orthotopic heart transplant (8) with postoperative chemotherapy; however, this has not been shown to change long-term outcomes. Future directions for treatment include immunologic therapies and autotransplant. (9)

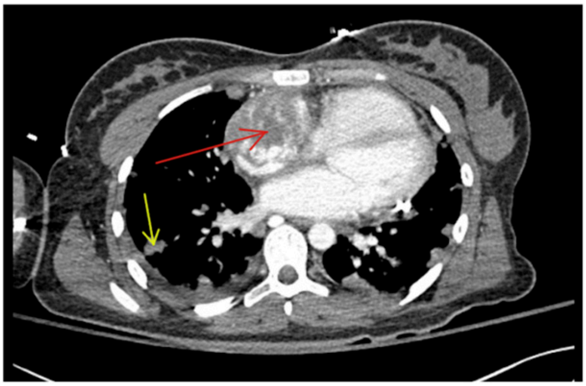

Figure 4. Patient's chest computed tomographic scan, axial view; red arrow indicates the primary tumor, and yellow arrow indicates lung metastases.

Treatment/Management

Surgical resection (if complete resection is possible), (10) chemotherapy (paclitaxel and neoadjuvant agents), radiotherapy, and palliative care consultation are advised.

Patient Course

The patient immediately underwent pericardiocentesis and was slowly weaned off vasopressors. She underwent cardiac catheterization with biopsy, and once the diagnosis was confirmed, she was started on emergent stereotactic body radiotherapy directed toward the right atrium and single-agent paclitaxel.

She recently completed stereotactic body radiotherapy divided into 5 fractions and 12 weeks of chemotherapy with paclitaxel. Her week 7 CT scan showed interval resolution in most of her pulmonary metastases and a decrease in primary tumor size by approximately 1 cm in every dimension. However, her latest CT scan, after paclitaxel therapy, shows progression of some of her remaining pulmonary lesions and several new lesions. Primary cardiac tumor size was stable on this scan. Resection of the primary tumor is not being pursued at this time due to active metastatic disease. She will likely receive more radiotherapy and recently began immunomodulatory therapy with an anti-PD1 monoclonal antibody (nivolumab) and an anti–CTLA-4 antibody (ipilimumab).

Lessons for the Clinician

- In a pediatric population, vasovagal syncope and orthostatic hypotension are more common than cardiac causes of syncope. Cardiac (electrical and structural) causes of syncope are rare (11) but can be life-threatening.
- Primary cardiac tumors can cause obstruction of circulation or poor venous return depending on location, resulting in symptoms of right heart failure.
- Because malignant primary cardiac tumors are likely to have metastases on presentation, complete imaging is important for complete diagnosis.
- Surgical resection is often the treatment of choice if malignant primary cardiac tumors can be resected completely; however, some patients still develop recurrent disease (12)(13)(14) and may benefit from adjuvant chemotherapy and radiotherapy. (15)

References for this article are at http://pedsinreview.aappublications.org/content/40/1/37.

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Case 1: Syncope in a 16-year-old Girl

Arhanti Sadanand, Meagan Ladell and Kayleigh Fischer

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Index of Suspicion

2 A 2-year-old Girl with Difficulty Bearing Weight

Stephanie Vander-Plas, MD,* Ngozi I. Eboh, MD, FAAP, FHM*

Department of Pediatrics, Texas Tech University Health Sciences Center, Lubbock, TX

AUTHOR DISCLOSURE Drs Vander-Plas and Eboh have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 2-year-old girl is transferred to our facility due to the inability to bear weight. On the previous day, she had normal development and received her hepatitis A vaccine at her pediatrician's office. A complete blood cell count, electrolytes, liver function tests, kidney function tests, C-reactive protein level, erythrocyte sedimentation rate, and magnetic resonance imaging (MRI) of the lumbar spine performed before transfer were normal. Results of cerebrospinal fluid (CSF) studies, urinalysis, and creatine kinase measurement performed on arrival were normal. Her condition rapidly progressed to include truncal ataxia, nystagmus, and upper extremity weakness without deep tendon reflexes. Further evaluation confirmed the diagnosis.

DISCUSSION

Based on presentation and rapid progression, a diagnosis of Guillain-Barré syndrome (GBS) was entertained. An MRI of the brain and spine was obtained and showed abnormal enhancement along the nerve roots of the cauda equina. Nerve conduction studies showed decreased response of the proximal nerves. She received intravenous immunoglobulin and remained hospitalized for 6 days, with gradual improvement.

Differential Diagnosis

Our differential diagnosis initially included trauma due to an occult fracture, infection, tick paralysis, acute flaccid myelitis, and GBS. Findings from plain radiographs of her knee and pelvis, complete blood cell count, and CSF studies were normal, eliminating traumatic and infectious etiologies. There was no history of travel to regions with tick populations, and no ticks were present on the patient. There was also no history of recent illness, ruling out acute flaccid myelitis as a likely source. As the presentation evolved, GBS moved to the top of the differential diagnosis list.

The Condition

Guillain-Barré Syndrome. Because young children commonly present with symptoms such as leg pain, weakness, and inability to bear weight, GBS should be strongly considered in these patients. As the disease progresses, the torso, arms, and muscles of respiration become involved, and this can lead to respiratory failure. Children may also have autonomic dysfunction or intestinal ileus. (1) Guillain-Barré syndrome presents as an acute ascending paralysis, often provoked by a preceding illness, causing demyelination of peripheral nerves. Incidence ranges from 0.3 to 1.3 cases per 100,000 in patients younger than 18 years, with boys being 1.5 times more likely to be affected than girls. (2)

Diagnosis. Primarily a clinical diagnosis, ancillary testing is used only to confirm the diagnosis. Testing includes CSF studies (elevated protein level with a normal white blood cell count), electromyography, MRI of the spine (shows enhancement of nerve roots and cauda equine [3]), and antibody studies. (4)

Management. With treatment, the course of the illness lasts approximately 2 to 4 weeks, a shorter duration than in most adults. (5) Treatment includes close monitoring and supportive care. (4) Immunologic treatment, including intravenous immunoglobulin and/or plasmapheresis, should be considered in severe, progressive cases. (5) Corticosteroids are ineffective. (6) We did not believe that her symptoms were due to the hepatitis A vaccine. A study in 2012 regarding the topic of hepatitis vaccination and GBS found the incidence to be similar to that seen in the general population, indicating that there is unlikely to be a link between the two. (7) As clinicians, it is imperative that we educate our patients on the necessity and benefit of vaccinations, as well as the extreme rarity of vaccine complications.

Lessons for the Clinician

- In patients who present with lower extremity pain, weakness, and inability to walk, Guillain-Barré syndrome should be strongly considered.
- Although mild cases may simply need observation and supportive care, early diagnosis and treatment of rapidly progressive cases is critical to prevent respiratory compromise.
- Guillain-Barré syndrome is a rare complication of only a few vaccines, and the benefits outweigh the risk in most cases; there does not seem to be a link between this syndrome and hepatitis vaccination.

NOTE. This case is based on a presentation by Stephanie Vander-Plas, MD, and Ngozi Eboh, MD, at the Pediatric Hospital 2017 Conference, Nashville, Tennessee, Poster Session #1, Poster #154, July 20,2017.

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Case 2: A 2-year-old Girl with Difficulty Bearing Weight

Stephanie Vander-Plas and Ngozi I. Eboh

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Index of Suspicion

3 An 11-month-old Boy with New Bradycardia

Christin T. Folker, MD,* Joseph W. May, MD, MPH*

Department of Pediatrics, Walter Reed National Military Medical Center, Bethesda, MD

AUTHOR DISCLOSURE Drs Folker and May have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 11-month-old boy is brought to the emergency department for 1 day of decreased appetite, vomiting, and diarrhea. His parents have both been ill with similar symptoms, and the boy tests positive for norovirus. In the course of his evaluation, he is found to be significantly bradycardic, with a heart rate varying from 55 to 65 beats/min. His parents report an uneventful prenatal and birth history, and he has since been a healthy child. Notably, recorded heart rates were age appropriate at all previous health maintenance visits.

On examination he is fussy but consolable and is in no distress. He is afebrile, with a normal blood pressure and respiratory rate for age. He is attentive and interactive. His head is atraumatic and normocephalic, with a soft and flat anterior fontanelle. His pupils are equal, round, and reactive to light. His mucous membranes are moist, and he makes tears when he cries. Radial, brachial, and femoral pulses are of normal strength. Cardiac auscultation confirms a heart rate of 65 beat/min, a regular rhythm, and normal S1 and S2 sounds with physiologic splitting. There are no murmurs or extra heart sounds. His distal extremities are well-perfused and have a capillary refill time of less than 2 seconds. His lung fields are clear. His bowel sounds are hyperactive, and his abdomen is without hepatosplenomegaly. He has no rashes. His neurologic examination findings are grossly normal. An electrocardiogram (ECG) is ordered to further assess his bradycardia (Fig 1).

DISCUSSION

Differential and Actual Diagnoses

This ECG may appear at first glance to show sinus bradycardia; however, closer examination of the patient's ECG reveals a variable PR interval and unusual and varying T-wave morphology, best noted in the lead II rhythm strip. The notching of the T waves occurs because of P waves (atrial depolarization) falling on T waves (ventricular repolarization). Our differential diagnosis focused on the following 3 categories as the etiology of this notching: atrial depolarization occurring too early, ventricular repolarization occurring too late, and atrioventricular (AV) block.

Early atrial depolarization could be caused by either an early sinus beat or an ectopic atrial focus. In the case of a premature atrial contraction (PAC), we would typically see a P wave arriving earlier than expected, along with variation in P-wave morphology, neither of which was apparent in this patient. Moreover, PACs that

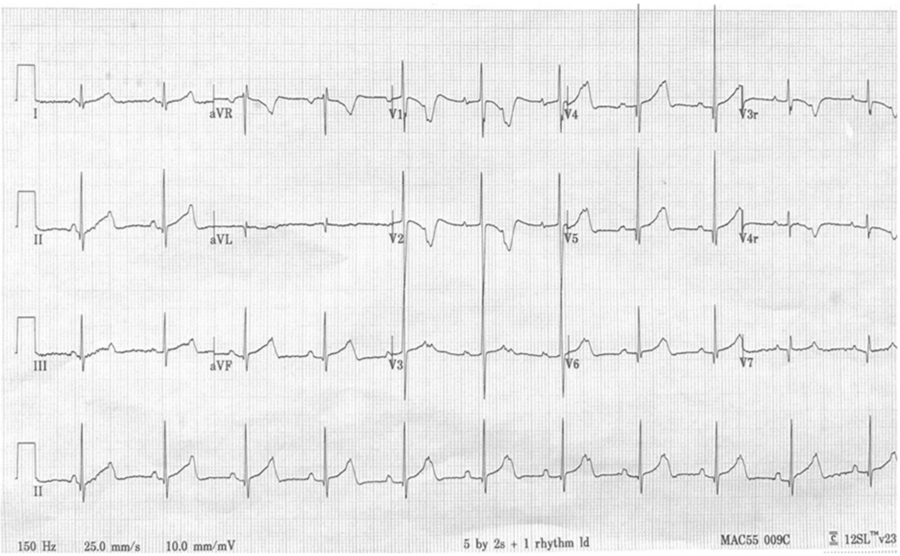

Figure 1. Electrocardiogram obtained at the time of presentation to the emergency department shows a narrow complex rhythm at a bradycardic rate for age (65 beats/min). Close examination reveals an inconsistent PR interval, along with variable notching of the T waves caused by buried P waves. The axis is normal for age, and the QTc is not prolonged (0.42 seconds). This image is consistent with third-degree atrioventricular block with a junctional escape rhythm.

occur during ventricular repolarization may fall in the absolute refractory period and fail to conduct (blocked PAC) or in the relative refractory period and conduct, albeit with slowed ventricular depolarization represented as a widened QRS complex (PAC with aberrancy). In this patient's ECG, even P waves occurring late in the T wave fail to conduct, making PACs an unlikely cause of the patient's abnormal ECG findings.

Prolonged ventricular repolarization would be seen on ECG as a long QT interval. In this case, normally timed atrial depolarization may occur before the completion of repolarization from the previous ventricular beat. This can be seen in patients with long QT syndrome or rarely from electrolyte disturbances or medication effect. In this patient, the corrected QT interval measured 0.42 seconds, falling in the normal range and eliminating late ventricular repolarization from the differential diagnosis.

P waves can also fall on T waves in various degrees of AV block. In Mobitz types I and II second-degree AV block, the nonconducted P wave can overlap the T-wave complex; however, typical Mobitz I and II patterns are not seen on this patient's ECGs. In 2:1 AV block, every second P wave is nonconducted and can fall on the T wave, and the conducted P wave does so at a normal and consistent PR interval. Second-degree 2:1 block seems unlikely for this patient's ECG, given the slight variability in the PR interval that is noted; however, this could be confirmed by examining more extended rhythm monitoring.

In third-degree AV block, P waves can fall on T waves arbitrarily, due to complete dissociation between atrial and ventricular depolarization. This diagnosis can be confirmed by assessing relatively consistent P-P and R-R intervals independently. This patient's P waves march out at consistent 0.46-second intervals, which would correspond with an appropriate heart rate of 130 beats/min (Fig 2A). The QRS complexes march out at 0.92-second intervals (corresponding with the recorded heart rate of 65 beats/min) and are narrow complex with a normal axis for age. This finding makes third-degree AV block with a junctional escape rhythm the most likely explanation for this child's bradycardia.

The Condition

Third-degree AV block most commonly occurs in infants and young children with complete congenital AV block (CCAVB), often the result of maternal antibodies cross-reacting with fetal conduction tissue in neonatal lupus. Anti-Ro (SSA) and anti-La (SSB) are the most common associated serologic markers. This patient had no clinical features of neonatal lupus, and both he and his mother tested negative for these antibodies. Along with his previously normal heart rates for age, this makes CCAVB unlikely.

Acquired AV block has a broad differential diagnosis, including infectious, genetic, and idiopathic etiologies. The patient had no family history of rhythm abnormalities, pacemaker placement, or myopathies. Echocardiogram showed normal anatomy with mild left ventricle enlargement. Of note, there was no left atrial isomerism or

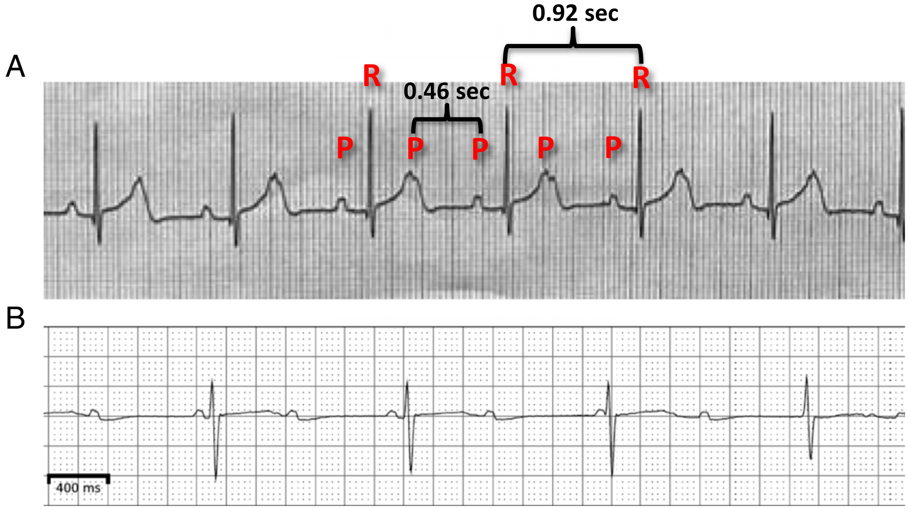

Figure 2. A. Electrocardiogram tracing taken from the lead II rhythm strip in Fig 1. "P" and "R" designate P and R waves, respectively. The patient's P waves march out at 0.46-second intervals, and the narrow QRS complexes march out at 0.92-second intervals. B. A separate electrocardiogram tracing taken from the same patient during his hospital stay more clearly demonstrates the complete dissociation between the P and R wave complexes that is typical for third-degree atrioventricular block. The patient's junctional escape rate is 40 to 45 beats/min at the time of this tracing.

L-transposition of the great arteries. Biventricular function was normal, with left ventricular ejection fraction of 70%, likely demonstrating a physiologic compensatory increase in stroke volume to maintain cardiac output. This high ejection fraction supported the hypothesis that his AV block had been present for some time, likely well before his acute norovirus symptoms.

A comprehensive evaluation for evidence of infectious etiologies (including *Borrelia burgdorferi*, mycoplasma, cytomegalovirus, rubella, influenza A and B, Coxsackie, echovirus, and adenovirus) as well as a chromosomal microarray and a 105-gene cardiomyopathy panel were negative. After an extensive evaluation, the diagnosis of acquired AV block was deemed to be idiopathic and coincidental to his norovirus infection.

Natural History and Treatment

The decision to place a permanent pacemaker can be complicated in young children, especially when the underlying cause of acquired AV block is unknown. Given the absence of randomized trials investigating pacemaker placement in young children, most recommendations are based on 2008 consensus guidelines that recommend pacemaker placement in pediatric patients with 1) advanced and symptomatic second- or third-degree AV block, 2) sinus node dysfunction causing symptomatic bradycardia, 3) persistent postoperative second- or third-degree AV block, or 4) CCAVB with wide QRS escape rhythm, complex ventricular ectopy, ventricular dysfunction, or a ventricular rate less than 55 beats/min. (1) None of these immediate indicators applied to our patient.

Given the patient's young age and small size, transvenous pacemaker placement would put him at increased risk for venous obstruction, (2) so epicardial (surgical) placement would be preferred. He would likely need additional surgical modifications to the device and leads as he grew. Considering this and the patient's current stability, the family and cardiology team made a shared decision to delay device placement with close cardiology follow-up.

Using the natural history of CCAVB as a proxy for this patient's anticipated course, we expect that he will require a pacemaker in the future. Patients with CCAVB typically experience decreasing ventricular rates over time and can begin to experience symptoms such as anxiety, poor school performance, sleep disturbances, and syncope at any age. (3) (4) Over time, echocardiography may show left ventricular dilation, abnormal wall stress, and AV valve dysfunction. Placement of a transvenous pacemaker later in childhood can often alleviate these findings, and the 2008 consensus guidelines support doing so electively for children and adolescents (class IIb recommendation). (1)

Patient Course

The patient was admitted to the hospital to monitor his trajectory. His electrolytes and inflammatory markers were normal, and he quickly recovered from his gastroenteritis symptoms. Ongoing telemetry more clearly confirmed the diagnosis of third-degree AV block (Fig 2B). His heart rate varied from 44 beats/min during sleep to 80 beats/min during peak activity. More than 52 hours of periodic ambulatory rhythm monitoring was analyzed on follow-up and demonstrated an average heart rate of 59 beats/min. The slowest recorded heart rate was 44 beats/min without any superimposed pauses. There were no instances of wide complex escape rhythm, ventricular ectopy, or ventricular arrhythmia to prompt early pacemaker placement. One year later, he remains in a stable junctional escape rhythm and is being closely monitored for eventual pacemaker placement.

Summary

On presentation with unexplained bradycardia, this child had an electrocardiogram (ECG) performed that could easily be mistaken for sinus bradycardia at first glance. However, much like the saying "even a broken clock is right twice a day," the patient's atrial rate, which was nearly twice the junctional escape rate, aligned on this ECG in such a way that simply gave the illusion of sinus conduction. Closer examination reveals abnormal PR variability and T-wave notching from buried P waves. These clues led to the final diagnosis of acquired third-degree atrioventricular block, which was deemed to be idiopathic in nature.

Lessons for the Clinician

- Acquired third-degree atrioventricular (AV) block, although less common in young children than congenital AV block, should be included in the differential diagnosis for bradycardia in pediatric patients.
- Abnormal T-wave morphology on electrocardiogram should alert the clinician to consider repolarization abnormalities, along with premature atrial contractions, long QT syndrome, and AV block.
- The decision to place a permanent pacemaker in a young child is complicated, with major indicators including the presence of symptoms or an unstable escape rhythm (among others).

Note. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or US Government.

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4 Weight Loss and Cough in a 12-year-old Boy

Peter J. Holmberg, MD,* Eugene Owusu-Achaw, MB, BM BCh,†
Adoma Dwomo-Fokuo, MB, BM BCh†

*General Pediatric and Adolescent Medicine, Mayo Clinic Children's Center, Rochester, MN
†Department of Pediatric Medicine, Dormaa Presbyterian Hospital, Dormaa-Ahenkro, Brong Ahafo, Ghana

AUTHOR DISCLOSURE Drs Holmberg, Owusu-Achaw, and Dwomo-Fokuo have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 12-year-old boy presents with 2 to 3 months of worsening cough and increasing fatigue. He is known to be retroviral positive and had been started on antiretroviral therapy 10 months earlier. At that time, he presented with fatigue and substantial weight loss of unclear amount, and it was discovered that his mother had recently died of AIDS. A rapid diagnostic test using an oral fluid sample was obtained and was positive for human immunodeficiency virus (HIV). He was started on antiretroviral therapy with zidovudine, lamivudine, and efavirenz, along with cotrimoxazole. He had weight gain and a decrease in symptoms after initiation of therapy, and, given his progress, his grandmother stopped his medications after 2 months of treatment.

On physical examination, he appears wasted and has a heart rate of 120 beats/min, a respiratory rate of 40 breaths/min, and a temperature of 98.4°F (36.9°C). He has thrush of the oropharynx and cervical lymphadenopathy. Auscultation of the lungs reveals diffuse crackles and coarse sounds. He has mild intercostal retractions, frequent cough, and the presence of digital clubbing. A chest radiograph was obtained and revealed bilateral perihilar adenopathy and innumerable widespread micronodular infiltrates throughout both lungs (Fig). A rapid test of a body fluid reveals the diagnosis.

DISCUSSION

Using morning gastric aspiration, a nucleic acid amplification test was positive for *Mycobacterium tuberculosis* and negative for rifampin resistance. Four-drug antituberculous therapy was initiated.

The Condition

Tuberculosis (TB) is an infectious disease caused by *M tuberculosis* and affects almost one-third of the population worldwide. In 2015, it is estimated that there were a total of 10.4 million new cases of TB. The following year, more than 25,000 children are estimated to have become newly infected. (1)(2) A disproportionate share of the disease burden is found in developing countries. These locations account for 95% of infections and 98% of mortality due to TB. (3) In children, limitations in diagnosing TB have resulted in significantly fewer

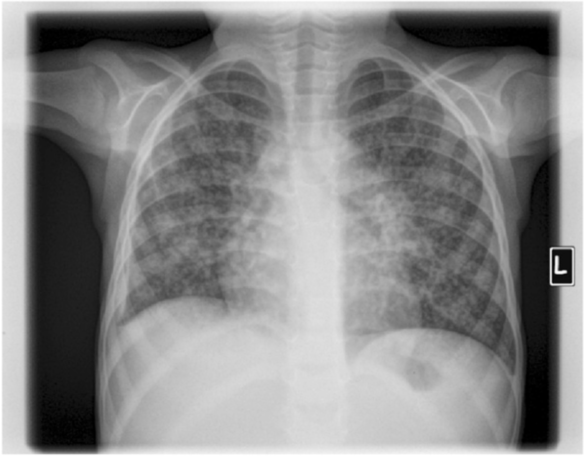

Figure. Chest radiograph revealing innumerable diffuse micronodules throughout both lungs along with bilateral perihilar adenopathy, left greater than right.

confirmed cases than actually occur. (2) This results in a lack of treatment for many children. The greatest risk of missed diagnosis is in children younger than 5 years, an age group that is responsible for half of all pediatric TB. (4) As a result, there is likely "a large and invisible burden of preventable child deaths related to tuberculosis." (5)

Human immunodeficiency virus has had a profound effect on TB and continues to significantly alter the acquisition, transmission, and progression of tuberculous disease. (6)(7) This burden is especially pronounced in sub-Saharan Africa, where up to 80% of HIV/TB co-infections take place. In some African countries, 60% to 70% of new TB cases are in individuals with HIV. (3)(7)(8) The diagnosis of TB in HIV-infected individuals can be more difficult as skin testing and acid-fast bacilli smears are more likely to be falsely negative. Even in children with accurately diagnosed TB, those with HIV face a markedly higher mortality rate and an increased incidence of drug-resistant TB. (5)(6)

A systemic form of disease characterized by diffuse nodular tubercles has been labeled "miliary TB" due to the millet seed appearance of tubercles on roentgenography. Spread via the lymphohematogenous route, miliary TB can involve numerous organs and cause wide-ranging signs and symptoms related to the involved systems. Although rare in immunocompetent individuals, children with advanced HIV have a much higher likelihood of miliary disease. (9)

Differential Diagnosis

In TB-endemic areas, in children who present with chronic cough, weight loss, and possible exposure, a diagnosis of TB should be strongly considered. In similar clinical presentations, other possibilities include *Pneumocystis jiroveci* pneumonia, atypical pneumonia, fungal infection, or an oncologic process. In addition, the chest radiographic findings could suggest Langerhans cell histiocytosis, viral pneumonia, hypersensitivity pneumonitis, pulmonary hemosiderosis or metastatic disease. CD4 counts can also be helpful when considering opportunistic infections. In general, the susceptibility to different infections correlates well with $CD4^+$ levels. For example, *Candida* infection is more common when the CD4 count drops below 300 cells/mm^3, whereas *Pneumocystis* and *Toxoplasma* infections are more likely after levels reach 200 cells/mm^3 and 100 cells/mm^3, respectively.

Diagnosis

The diagnosis of TB infection in children is difficult. Historically, sputum smears have been the standard method of identification. However, this is complicated by several factors. Children of young age are often unable to expectorate adequate sputum for sampling. Methods aimed at improving specimen collection include gastric aspiration and sputum induction. (10) Tuberculosis is often paucibacillary, and even adequate sputum samples may have too few bacilli present for diagnosis. (7) Skin testing and interferon-γ release assays are tests that use an individual's natural immune response to *M tuberculosis* infection and are used in many areas of the world. Nucleic acid amplification testing (NAAT) is a relatively new technology in TB diagnosis and uses polymerase chain reaction. A specific cartridge-based NAAT has been recommended by the World Health Organization for use in children, a test that is also able to simultaneously test for rifampin resistance. Last, culture of *Mycobacterium* remains the gold standard of diagnosis but has significant limitations of its own. (11)

The diagnosis of miliary TB requires a high level of clinical suspicion. Signs and symptoms of miliary TB can be very nonspecific. Although fluid, tissue, and blood are extremely helpful in confirming systemic involvement, in settings where TB is endemic, clinical diagnosis is often the only method available. In these situations, the diagnosis of miliary TB can be made if a child has symptoms of TB, confirmed TB infection (based on the testing available), and classic miliary findings or diffuse reticulonodular lesions on imaging. (12)(13)

Treatment

First-line treatment for active, susceptible TB remains a 4-drug regimen using rifampin (RIF), isoniazid (INH), pyrazinamide, and ethambutol for a defined interval, followed by INH and RIF for 18 additional weeks. In situations where children are unable to undergo routine eye testing, ethambutol is often foregone unless evidence of upper lobe disease is present. (14) Resistance to first-line antituberculous drugs has become a widespread problem. Tuberculosis that is resistant to INH and RIF is considered multidrug-resistant TB (MDR-TB), and additional resistance to an injectable agent and any fluoroquinolone is described as extensively drug-resistant TB. (15) According to the World Health Organization, there were almost 500,000 total new MDR-TB cases in 2015. (1) Treatment of MDR-TB generally uses sensitivity-based treatment with a fluoroquinolone as well as an injectable agent. (16) Extensively drug-resistant TB treatment involves more drugs (5–6 organism-susceptible agents) for a longer duration (≥24 months after negative cultures) than other regimens. (17) Children with any form of resistant TB who do not get appropriate treatment have a high likelihood of death. (2)(9)(13)

Outcome

The patient in our case eventually succumbed to disseminated TB infection and died despite appropriate therapy. This case reveals the importance of early diagnosis and adequate and consistent therapy, as well as the role that HIV co-infection plays in worldwide TB.

Lessons for the Clinician

- TB is a leading cause of mortality worldwide and is of particular importance in children affected by HIV.
- Drug-resistance to first- and second-line anti-TB agents is becoming a serious complicating factor in the treatment of individuals with TB infection.
- TB must be considered when caring for children with adequate exposure history and other risk factors such as HIV infection or other immune-suppression.
- TB commonly presents with hilar adenopathy on chest radiograph and the presence of diffuse micronodules is often specific to miliary TB.

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Case 4: Weight Loss and Cough in a 12-year-old Boy

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in Brief

Ear Piercing

Jillian Parekh, MD,* Faye Kokotos, MD*
**Children's Hospital at Montefiore, Bronx, NY*

AUTHOR DISCLOSURE Drs Parekh and Kokotos have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Ear piercing is a very common practice among cultures throughout the world; however, significant disparities exist about when to pierce ears and how often families involve their pediatricians in making this decision. When families do choose to involve their provider, there are some important elements to discuss with them about the timing and possible complications of ear piercing.

The timing of ear piercing can often be influenced by a family's culture or traditions. The American Academy of Pediatrics' (AAP's) most recent writing on this topic dates back to 2004 and notes, "…as a general guideline, postpone the piercing until your child is mature enough to take care of the pierced site herself." Like many parenting and medical decisions, the question of timing is one of risk versus benefit. The AAP further advises, "…if the piercing is performed carefully and cared for conscientiously, there is little risk, no matter what the age of the child." When deciding to go ahead with ear piercing, families should be aware of its known complications, which include unwanted cosmetic effects, foreign body aspiration, allergy sensitization, and infection. One study found that up to 35% of people with pierced ears experienced 1 or more complications.

The earlobe is one of the more common sites for hypertrophic scarring, or keloid. Although the pathogenesis of keloid formation is poorly understood, African Americans and people with a family history are at higher risk. A study in 2005 also notes an increased risk of keloid formation with piercings performed after age 11 years. Treatment regimens may involve intralesional corticosteroids, cryotherapy, and surgical excision; however, recurrence is common. Given the limited success of treatment, a family or personal history of keloid should be taken into consideration when deciding whether to pierce ears.

Trauma to a pierced ear is also a frequent complication, with lacerations ranging from accidental pulling of the earring through the earlobe to injury from a fall, contact sport, or motor vehicle accident. Any such wound should be cleaned and repaired within 12 to 24 hours. In addition, wearing heavy earrings can result in deformities to the earlobes. Pediatricians and families should discuss safe earring choices and removal of jewelry during contact sports.

Another complication to consider is the possibility of the earring becoming embedded in the earlobe, especially if the lobe is thick, is fleshy, or was pierced with a spring-loaded gun. Usually the backing of the earring becomes embedded: strong and constant pressure from the earring may lead to ischemia of the skin, which then becomes inflamed and allows the backing to penetrate into the earlobe. Embedding may be prevented by using longer earring posts with adjustable backings. Removal of the embedded earring or backing involves gentle probing, but may sometimes require surgical excision.

Infants and young children are at risk for ingesting and aspirating small earring pieces. An earring aspirated into the airway may present with cough,

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stridor, or wheezing. One way to prevent aspiration or ingestion is to discourage the wearing of earrings in infancy through 4 years of age, when the risk is the greatest. Another preventive strategy is to recommend earrings with locking or screw-on backs, which require adult assistance to unfasten.

Earrings are also associated with allergic contact dermatitis. Nickel is one of the most common triggers, and exposure is almost unavoidable because nickel is found in many everyday items, such as jewelry, belt buckles, jean snaps, and coins. Allergy to nickel is increasing in prevalence worldwide, especially among children: 26% of all patch tests are positive for nickel sensitivity. Risk factors for developing allergy to nickel include female sex, young age, and body piercing, with body piercings, especially pierced ears, posing the most significant risk. Nickel allergy most commonly presents as a localized dermatitis in the area of greatest contact with nickel, but it can also cause an id reaction, with spread of the rash to sites distant from exposure. Treatment involves removing the offending agent, with symptomatic relief from mid- to high-potency topical corticosteroids, antihistamines for pruritis, and moisturizers that aid in repairing the skin barrier. Prevention depends on avoiding piercings with nickel-containing jewelry, especially earrings.

Infection after piercing is infrequently reported in the medical literature and generally is less severe with ears than with other body piercings. Infections can be introduced both at the time of the actual piercing, if done with poor sterile technique, and during aftercare if the wound is not kept clean. *Staphylococcus aureus* is the most commonly reported bacteria, followed by group A β-hemolytic streptococci. *Pseudomonas aeruginosa* is most common in piercings that involve the auricular cartilage. Infections range from superficial to abscess formation. Treatment involves topical antibiotics for superficial infection, oral antibiotics when the infection is more extensive, and incision and drainage for an abscess. Viral infections, especially involving the spread of hepatitis B and C, have also been reported. Although there are no data specifically supporting the recommendation, many pediatricians urge postponing ear piercing until completion of the initial tetanus-containing vaccine series. As part of their counseling, pediatricians should discuss the risks of infection when consulting about piercings.

Once the decision has been made to have a child's ears pierced, families should be urged to follow the AAP's simple recommendations for safe care. The piercing should be performed by a doctor, nurse, or experienced technician, with a disinfectant, such as rubbing alcohol, applied to the earlobe to minimize the chance of infection. A round gold-post earring is best for the initial piercing. Rubbing alcohol or an antibiotic ointment should be applied to the pierced area twice a day for a few days after the piercing. The earrings should be rotated gently every day, and the initial pair should not be removed for 4 to 6 weeks.

Although complications from ear piercing do exist, they can generally be avoided with proper care. Decisions about whether to pierce a child's ears include many cultural, familial, and medical factors. Pediatricians should be prepared to help educate and guide families to make this process safe.

COMMENT: Years ago, when our son was in his early teens, my wife and I were pleased that he opted to have his ears pierced, when he might have chosen some more risky way to express his independence. I bring this up only because **he** might wonder why the AAP guideline quoted in this *In Brief* suggests waiting "…until your child is mature enough to take care of the pierced site **her**self." Even back in 2004, when the guideline was published, boys too quite commonly had their ears, and other body parts, pierced—let's not leave them out of our counseling.

– Henry M. Adam, MD
Associate Editor, *In Brief*

ANSWER KEY FOR JANUARY 2019 PEDIATRICS IN REVIEW

Sleep-Disordered Breathing in Children: 1. C; 2. A; 3. D; 4. E; 5. D.
Acute Myocarditis and Pericarditis in Children: 1. A; 2. C; 3. E; 4. E; 5. B.
Rationale for the Immunization Schedule: Why Is It the Way It Is?: 1. C; 2. D; 3. E; 4. A; 5. E.

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Visual Diagnosis

Teenager with Fever, Petechiae, Confusion, and Weakness

Senthil Velan Bhoopalan, MD, PhD,* Rupesh Kumar Natarajan, MD,†
David Di John, MD†

*Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN
†Department of Pediatrics, University of Nevada School of Medicine, Las Vegas, NV

PRESENTATION

A 13-year-old previously healthy girl presents with fever (101.5°F [38.6°C]) for 3 days. It was preceded by generalized headache. The patient reports no history of vomiting, difficulty breathing, coughing, chest pain, blurry vision, speech disturbance, or trauma. The patient also has diffuse muscle pain, although no swelling of limbs or limitation of activity is reported. There is no history of any recent travel, sick contacts, or exposure to animals or insects. She does not report any intravenous drug abuse. Her dental braces were adjusted 2 weeks before admission. Our patient has no previous medical or surgical history. There is no family history of any congenital heart defects, arrhythmia, or frequent infections. She lives with her parents and has a 31-year-old brother, who is healthy.

In the emergency department she has a temperature of 102°F (38.9°C), with associated tachycardia but otherwise normal vital signs. Her physical examination shows an ill-appearing young febrile girl who is alert and oriented to time, place, and person but has trouble recalling events that happened in the past 5 to 7 days. Strikingly, there are multiple nonblanching petechial hemorrhages in the tips of her fingers and toes (Figs 1–3). In addition, tender nodes are appreciated in both palms and soles. The patient also has some weakness of all 4 limbs, but no other notable findings on clinical examination are appreciated. Importantly, auscultation of the heart reveals normal heart sounds with no murmurs. Initial laboratory data include a white blood cell count of 12,000/μL (12×10^9/L), a hemoglobin value of 13 g/dL (130 g/L), and a platelet count of $118 \times 10^3/\mu$L (118×10^9/L). The comprehensive metabolic panel is normal, but her C-reactive protein level and erythrocyte sedimentation rate are elevated at 130 mg/L (1,238 nmol/L) and 25 mm/hr, respectively. A blood culture and lumbar puncture are collected. Cerebrospinal fluid studies do not show any abnormalities. A transthoracic echocardiogram is performed that confirms the diagnosis.

DIAGNOSIS

The echocardiogram demonstrates mitral valve endocarditis and a mobile vegetation measuring 1.5 × 1 cm in the ventricular surface of the anterior leaflet of the mitral valve (Video 1). Although the patient has normal ventricular function, the vegetation causes some mitral incompetence (Video 2). The other valves are

AUTHOR DISCLOSURE Drs Bhoopalan and Natarajan have disclosed no financial relationships relevant to this article. Dr Di John has disclosed that he is principal investigator for AstraZeneca and Cempra Pharmaceuticals clinical trials research on new drugs to treat infections in children, and he is on the speaker's bureau for vaccine-related issues for Sanofi Pasteur. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

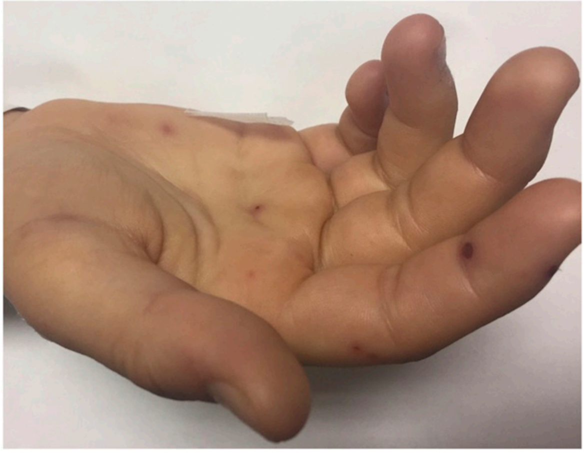


Figure 1. Macular lesions in the palm.

unaffected. The blood culture is positive for methicillin-sensitive *Staphylococcus aureus*. Due to the altered mental status and weakness of extremities, magnetic resonance imaging of the brain is performed and shows multiple ischemic areas in both cerebral hemispheres as well as a punctate ischemic stroke in the left cerebellum. No midline shifting, edema, or mass effect is reported. Our patient is diagnosed as having bacterial endocarditis caused by methicillin-sensitive *S aureus* and is treated with antibiotics.

DISCUSSION

Epidemiology

Infective endocarditis (IE) is less common in the pediatric population compared with adults. Reported incidence ranges from 0.3 cases (in older children and teenagers) to 3.3 cases (in infants) per 100,000 children per year. (1)(2) Although traditionally reported to be more common in children with congenital heart disease in developed countries, increased use of indwelling catheters is believed to contribute to a rise of IE in children without CHD. Another major pediatric population at risk for IE is newborn infants, even those with a structurally normal heart. A little more than 7% of pediatric patients with IE are neonates. There seems to be a bimodal distribution of IE with respect to age in children, peaking during infancy and again during late adolescence. (1)

The general clinical presentation is an indolent illness with nonspecific complaints such as fever, fatigue, weakness, myalgia, and sweating. This, coupled with the rarity of the condition in children, makes it a challenge to diagnose IE. (3)(4) Nevertheless, because previously healthy children without any risk factors can also develop IE (10%–20%), diagnosis requires a high degree of suspicion and a thorough physical examination. (2)(5)(6)(7)

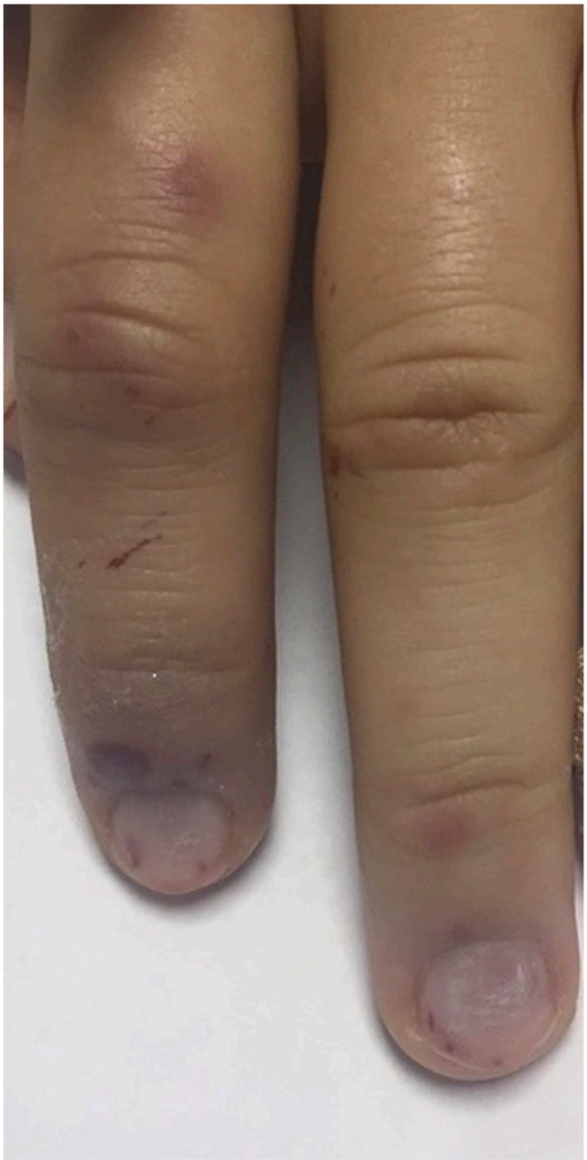


Figure 2. Splinter hemorrhage under the nail.

Causative Agents

The most common infectious agents implicated in IE are bacteria, especially gram-positive cocci. Viridans group streptococci and *S aureus* are the most common agents. Other causative agents include coagulase-negative staphylococci, *Streptococcus pneumoniae, Enterococcus* species, and HACEK (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species) organisms. Less frequently, group B *Streptococcus* species and gram-negative rods are also implicated. Fungal endocarditis, typically caused by *Candida albicans* and, rarely, *Aspergillus* species, is classically reported in children receiving parenteral nutrition.

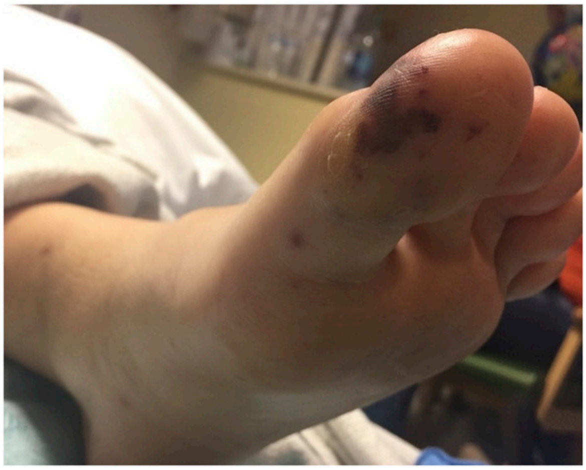


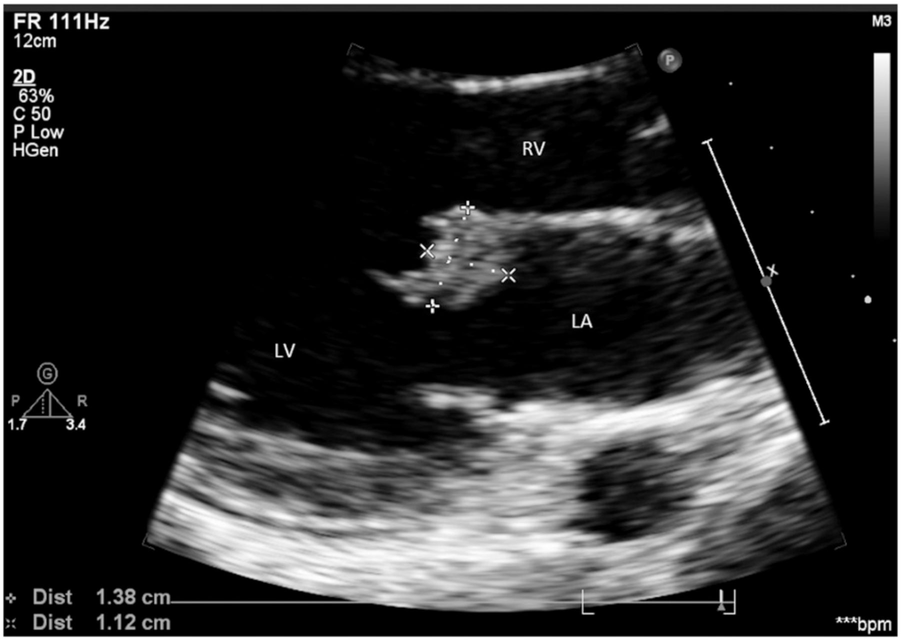
Figure 3. Purpuric lesions on the plantar aspect of the foot.

Pathogenesis

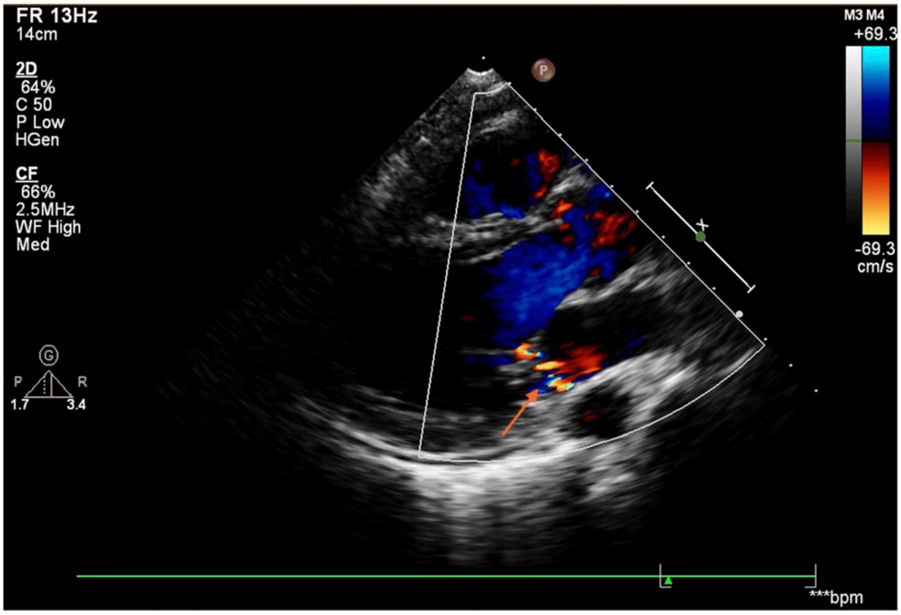
The pathogenesis of IE has been well-studied using animal models and observational studies in humans. The initial process for developing IE involves turbulent flow-mediated valvular damage. The turbulent flow may be due to a variety of reasons, such as intracardiac devices, prosthetic valves, peripherally inserted central catheters, and congenital heart disease. This turbulent flow-mediated damage results in formation of nonbacterial thrombotic endocarditis aided by a host response involving fibrin deposition and platelet activation. An initial bacteremia in the presence of a traumatized endothelium on the valve surface forms a nidus of infection. Current research suggests that inherited variations in genes encoding for inflammatory markers and cytokines could increase the risk of IE. The initial adhesion of bacteria to the damaged endothelial surface is aided by a multitude of pathogen-dependent factors, such as adhesions and pili, and by host-derived factors, such as collagen, laminin, fibrinogen, and fibronectin. In addition, as the bacteria multiply in number they begin forming a biofilm that creates a barrier for host immune cells and antibiotics to infiltrate the vegetation.

Clinical Presentation and Diagnosis

Although most patients present with an indolent history and nonspecific complaints, the occasional child will present with fulminant bacteremia and high spiking fevers. The clinical presentation is related to bacteremia, valvulitis, immune response, and septic emboli. Valvulitis and vegetations can present as new-onset cardiac murmurs, but patients usually present without any significant cardiac findings. Heart murmurs are reported in only 10% to 20% of patients with IE. (5)(6)(7)(8) Immunologic phenomena are primarily due to immune complex deposition and manifest as glomerulonephritis, Osler nodes (tender intradermal nodules on digits), and Roth spots (small retinal hemorrhages). Septic emboli can present as



Video 1. Parasternal long axis echocardiograph showing vegetation on the ventricular surface of the anterior mitral leaflet. LA=left atrium, LV=left ventricle, RV=right ventricle.



Video 2. Flow mapping of regurgitant jet (orange arrow) into the left atrium.

mycotic aneurysms, septic pulmonary infarcts, conjunctival hemorrhages, and Janeway lesions (painless hemorrhage on the palms and soles). Although fever is the most common presentation, symptoms such as heart failure and arthralgia, and signs such as splenomegaly, murmur, petechiae, and embolic phenomena, are noted in nearly 50% of pediatric patients. Complex and variable clinical manifestations make IE a diagnostic challenge. The Duke criteria are a validated tool to diagnose IE. The modified Duke criteria (Table) use pathological, clinical, echocardiographic, and laboratory findings to improve sensitivity. (9)

Patients with IE often have nonspecific laboratory findings, such as elevated white blood cell count, C-reactive protein level, and erythrocyte sedimentation rate and low complement levels. Blood culture is the most important investigation because it aids in diagnosis and guides treatment. Multiple blood cultures, with adequate volume for aerobic and anaerobic culture, are strongly recommended. In addition, patients should be evaluated with an echocardiogram. Although transesophageal echocardiography has better sensitivity, transthoracic echocardiography is less invasive and is usually performed first. In patients with suspicion for septic emboli, it is also ideal to obtain a magnetic resonance image of the brain.

Treatment

Antibiotics are the mainstay of treatment and should be started immediately. Broad-spectrum coverage with vancomycin and gentamicin is recommended until bacterial identification and sensitivity are established. Once sensitivity is determined, the antibiotic regimen should be narrowed and treatment continued for 4 to 6 weeks for uncomplicated infections. For patients with prosthetic valves, it is recommended to add rifampin for synergy and to treat for at least 6 weeks. Surgical intervention should be considered in patients with persistent infection and positive blood culture for more than 5 to7 days after starting appropriate intravenous antibiotics. Infective endocarditis remains a serious condition with significant morbidity and mortality, although recent mortality is improved compared with historical data. High mortality rates are associated with neonatal IE, IE due to fungus and *S aureus*, and poor ventricular function. Patients with a history of IE are considered to be at high risk for another IE and require antibiotic prophylaxis for procedures associated with bacteremia of IE-associated organisms.

PATIENT COURSE

Our patient continued to have persistent fevers, for which we added rifampin, as suggested by the infectious disease consultant. Cardiothoracic surgery was performed to remove the vegetation and repair the mitral valve, after which the patient improved significantly. She received antibiotics for a total of 8 weeks and has been doing well since discharge.

TABLE. **Modified Duke Criteria for IE (Pathological Criteria Not Shown)**

MAJOR CRITERIA
1. Blood culture positive for IE
A. Typical microorganisms consistent with IE from 2 separate blood cultures:
i. Viridans streptococci, *Streptococcus bovis,* HACEK group, *Staphylococcus aureus*; or
ii. Community-acquired enterococci in the absence of a primary focus; or
B. Microorganisms consistent with IE from persistently positive blood cultures defined as follows:
i. At least 2 positive cultures of blood samples drawn >12 h apart; or
ii. All of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn ≥1 h apart)
C. Single positive blood culture for *Coxiella burnetii* or antiphase 1 IgG antibody titer >1:800
2. Evidence of endocardial involvement
3. Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least “possible IE” by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
A. Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomical explanation; or
B. Abscess; or
C. New partial dehiscence of prosthetic valve
4. New valvular regurgitation (worsening or changing or preexisting murmur not sufficient)
Minor criteria
1. Predisposition, predisposing heart condition, or injection drug use
2. Fever, temperature >100.4°F (>38°C)
3. Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
5. Microbiologic evidence: positive blood culture, but does not meet a major criterion as noted above,[a] or serologic evidence of active infection with an organism consistent with IE
Definitive IE
1. 2 major criteria; or
2. 1 major criterion and 3 minor criteria; or
3. 5 minor criteria
Possible IE
1. 1 major criterion and 1 minor criterion; or
2. 3 minor criteria

*HACEK=*Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus, Haemophilus influenzae, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae, *and* Kingella denitrificans, *IE=infective endocarditis, TEE=transesophageal echocardiography, TTE=transthoracic echocardiography.*

[a] *Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.*

Adapted from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infectious endocarditis. Clin Infect Dis *2000;30(4):633–638.*

Summary

- Infective endocarditis is an uncommon but serious pediatric condition that requires a high degree of suspicion to diagnose.
- Infectious endocarditis has been reported in patients without any risk factors and even in the presence of normal cardiac examination findings. Most pediatric patients present with nonspecific signs and symptoms, which further highlights the importance of a thorough physical examination in children presenting with unexplained fever.
- Blood culture and echocardiography are the most important initial diagnostic tests. Empirical treatment includes vancomycin and gentamicin (with rifampin for patients with prosthetic valves) until culture and sensitivity results are available.

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Visual Diagnosis: Teenager with Fever, Petechiae, Confusion, and Weakness

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Understanding Unicameral and Aneurysmal Bone Cysts

Joseph Rosenblatt, DO,* Adrienne Koder, DO*

**St Christopher's Hospital for Children, Philadelphia, PA*

Practice Gaps

1. Recognizing benign vs malignant bone cysts on radiographs can be challenging.
2. Clinicians may not always recognize important historical and physical findings associated with bone cysts.
3. It is important for clinicians to know what tests need to be ordered and when to refer to a pediatric orthopedic specialist.

Objectives

After completing this article, readers should be able to:

1. Demonstrate a basic understanding of the etiology of unicameral bone cysts and aneurysmal bone cysts.
2. Identify radiographic findings of bone cysts and determine when to order advanced imaging.
3. Implement basic treatment protocols for bone cysts.

Abstract

Bone cysts in the pediatric population are often found incidentally on radiographs or after a cyst has created cortical weakness leading to a pathologic fracture. Most bone cysts are benign, are pain free, and resolve spontaneously. The most common bone cyst is unicameral 1-chamber bone cyst, also known as simple bone cyst. General practice pediatricians may be the first to encounter these lesions, and this article aims to help elucidate their incidence, etiology, clinical findings, radiologic findings, and modern treatment approaches. The other differential diagnoses that should be considered, specifically, aneurysmal bone cyst, are also explored. This summary is not all inclusive, and it is recommended that all patients be referred to a pediatric orthopedist.

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ABBREVIATIONS

ABC	aneurysmal bone cyst
MRI	magnetic resonance imaging
UBC	unicameral bone cyst

SIMPLE BONE CYSTS

Incidence

Simple bone cysts (also known as solitary bone cysts or unicameral bone cysts [UBC]) are benign tumors of childhood and adolescence. They represent approximately 3% of all biopsied primary bone tumors and commonly occur during the first 2 decades of life, most often between 4 and 10 years of age. (1)

Most cysts occur in the metaphyseal region of the proximal humerus or femur (Fig 1). The next most common sites are the proximal tibia and distal tibia. Occasionally, cysts may be found in the calcaneus, fibula, ulna, radius, pelvis, talus, lumbar spine, and other parts of the axial skeleton. Cysts that are pain free are generally benign, and those that have pain may be more likely to be malignant. Because it can be difficult to distinguish pain in the pediatric population, a good history and physical examination is vital to making the diagnosis.

S*olitary bone cyst* is an accurate term because rarely does more than 1 cyst occur in an individual. The term *unicameral bone cyst* implies that 1 chamber exists. Although 1 large cavity is usually found, a cyst may become multiloculated after a fracture because of the formation of multiple bony septations, thus making the term *unicameral* technically incorrect.

Simple cysts are often categorized as either active or latent according to Jaffe and Lichtenstein based on their distance from the growth plate. In general, patients with active cysts are younger, and active bone cysts have a higher rate of failure with treatment, regardless of treatment type. (2)(3)(4)(5) A cyst that is less than 0.5 cm from the physis is considered active and possesses greater potential for growth and subsequent fracture. In addition, an active cyst presents with the risk of expanding into and damaging the physis, ultimately causing growth arrest and deformity or limb-length inequality. Epiphyseal involvement is rare but if present it should be considered an aggressive form of an active lesion. (6) A cyst that has grown away from the growth plate is considered latent and theoretically no longer has the capacity for growth (Fig 2). However, latent cysts continue to have the potential for growth, as often seen by their unexpected recurrence after treatment in the young patient. (2) After skeletal maturity, however, it is uncommon for the cysts to recur or progressively worsen. Most commonly, latent cysts grow further from the physis as the bone grows, thus being less of a threat for deformity.

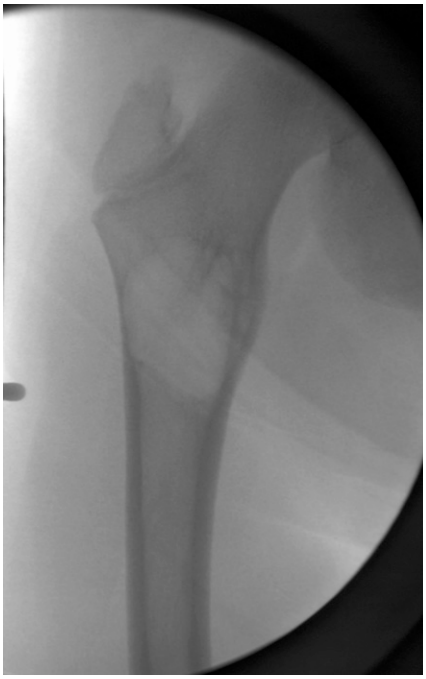

Figure 1. Radiograph of a 9-year-old boy with right groin pain showing a unicameral bone cyst in the proximal femur.

Etiology

The cause of simple bone cysts remains uncertain. To fully explain the etiology of simple bone cysts, a proposed theory should address the following factors: 1) more than 70% are discovered in childhood, 2) more than 95% arise from or involve the metaphysis, 3) most occur in the proximal humerus or femur, 4) a cyst wall and fluid high in protein content are common, and 5) simple bone cysts represent a benign process with a significant recurrence rate after treatment.

There are multiple hypotheses surrounding the formation of simple bone cysts. One proposition is that a synovial cyst with a small amount of synovial tissue becomes entrapped in an intraosseous position after birth trauma or during early development. Over time, increased pressure secondary to secretions leads to expansion of the cystic structure in the bone. (1) Others have postulated that cysts result from a localized failure of ossification in the metaphyseal area during periods of rapid growth. (4) Another popular proposed theory is that the cause of the cyst is blocked circulation (venous obstruction) and drainage of interstitial fluid in rapidly growing bone.(7) The last theory is based on the finding that the chemical constituents of the fluid in simple bone cysts are similar to those of serum. (8)

Furthermore, current literature further substantiates this theory of a blockage or occlusion of the intramedullary circulation. (9)(10)

Clinical Features

Most bone cysts found in the pediatric population will be found incidentally on a radiograph. More often, however, cysts are diagnosed because of pain. The pain may be mild and reflect a microscopic pathologic fracture. More abrupt

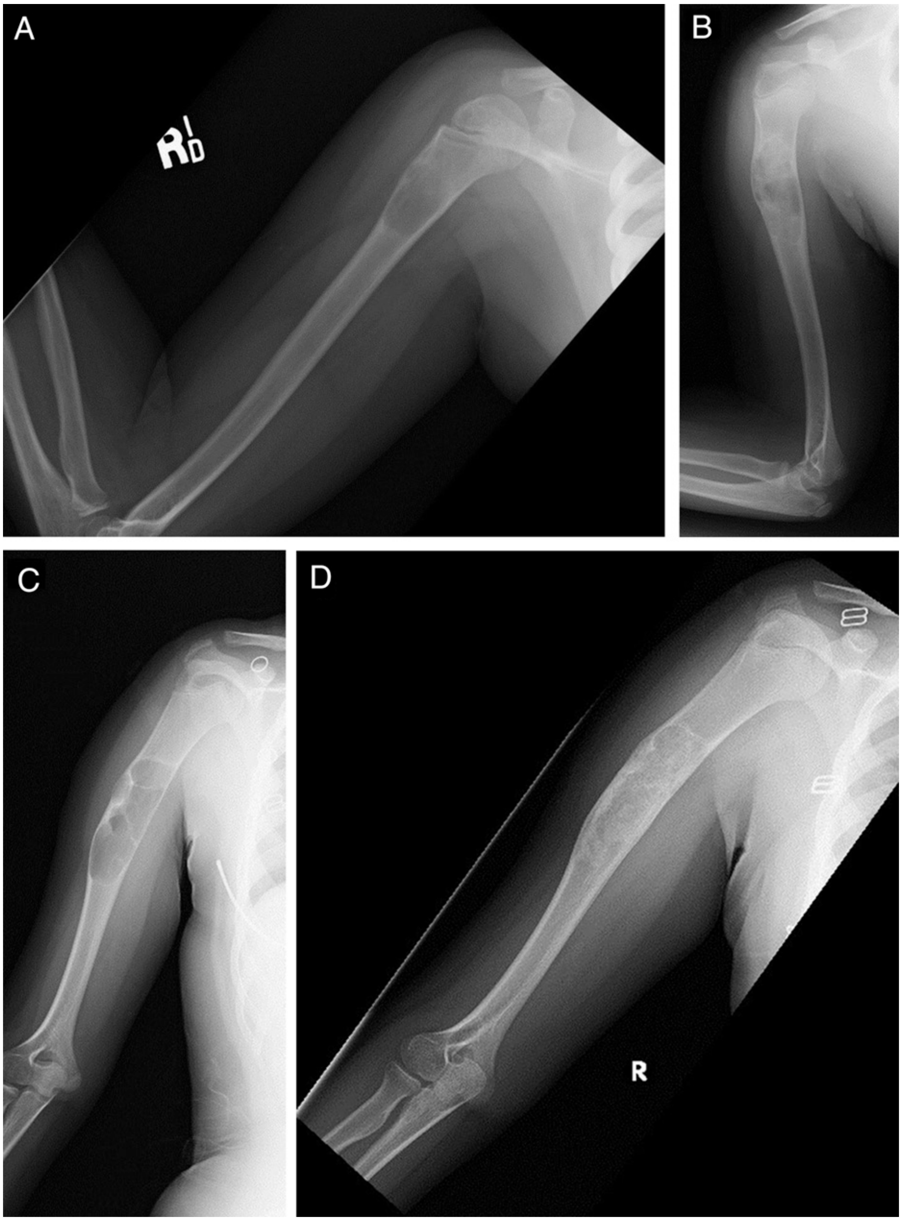

Figure 2. Radiographs showing a solitary cyst evolving from active to latent. A. At 7 years old. B. At 9 years old. C. At 11 years old. D. At 13 years old.

discomfort occurs when a pathologic fracture occurs after relatively minor trauma, such as a fall, throwing a ball, or even closing a car door. In this case a child can present with pain, swelling, erythema, and possibly a deformity. These fractures occur in up to 90% of patients and heal readily, although the cysts do not. (11) After these pathologic fractures, premature physeal closure has been reported in nearly 10% of patients. (12)

Physical Examination

The physical examination should include a focused evaluation of the tumor site, including evaluation for the presence of a mass, swelling, range of motion, effusion, and changes in temperature or color of the involved extremity. In addition, a complete examination of the patient is essential for ruling out secondary lesions, enlarged nodes, or skin changes, such as café-au-lait spots. It is imperative to rule out skin and soft tissue involvement, which would direct the differential diagnosis away from UBC.

Radiographic Findings

Simple bone cysts have several characteristic radiographic features. Their radiographic appearance is so typical that most can be diagnosed without a biopsy.

Approximately 50% occur in the proximal humerus and up to 30% in the proximal femur. The cyst is metaphyseal and usually extends to, but not across, the physis. On rare occasions it can cross the physis into the epiphysis. (13) Typically the cyst is symmetrically expansile and radiolucent, with a thin cortical rim. Over time the physis grows away from the cyst. In many newly diagnosed patients a pathologic fracture occurs with or without displacement. The 1 pathognomonic sign of a simple bone cyst is the "fallen leaf" fragment (Fig 3A) (14) This represents a portion of fractured cortex that settles to the most dependent part of the fluid-filled cyst. However, it is seen in less than 10% of patients, and it should not be expected if the cyst has become multiloculated after a previous pathologic fracture.

Simple bone cysts that have undergone healing after pathologic fracture have a complex appearance on magnetic resonance imaging (MRI) because the previous fracture causes heterogeneous fluid signals and areas of thick peripheral rim enhancement. (11) An MRI may also detect fluid levels, soft tissue changes, and septations not seen on plain film.

Differential Diagnosis

The diagnosis can usually be established based on the presence of typical radiographic findings. Other lesions to be considered in the differential diagnosis include aneurysmal bone cyst (ABC), monostotic fibrous dysplasia, atypical eosinophilic granuloma, endochondroma, and intraosseous ganglia. All these lesions may be radiolucent. Knowing the defining radiologic appearance of these lesions will aid the clinician in differentiating them from simple bone cysts. Both fibrous dysplasia and ABCs may be in the metaphysis and appear expansile; however, ABCs are more commonly eccentric, where fibrous dysplasia has a "ground glass" appearance and is typically a central lesion.

Enchondromas are well-defined, radiolucent, central medullary lesions that often appear more diaphyseal as a long bone grows. Enchondromas may be associated with cortical thinning and expansion in short tubular bones of the hands and feet, but not in long tubular bones (femur, tibia). Typically found incidentally, intraosseous ganglia are small, well-demarcated radiolucent lesions with a well-defined sclerotic rim in the epiphyses and subchondral region of long bones. (9)

Treatment

Nonsurgical treatment with observation is reasonable for small and asymptomatic UBCs, particularly those in the upper extremity or calcaneus. The main indications for surgical intervention are continued pain, impending/recurrent fracture, and prevention of secondary deformity. (15) A common misconception in the treatment of simple bone cysts in children is that once the pathologic fracture heals, the cyst also has an excellent chance of healing spontaneously. Investigators examining this phenomenon have found that the likelihood of spontaneous healing of the cyst after pathologic fracture is very low, probably less than 5%. (3)(14)(16) Thus, if treatment of the cyst is deemed necessary, it should be undertaken as soon as the fracture has healed. However, overtreatment in skeletally mature persons should be avoided. In these individuals, if the cyst has a sufficiently thick cortex and is located in the upper extremity,

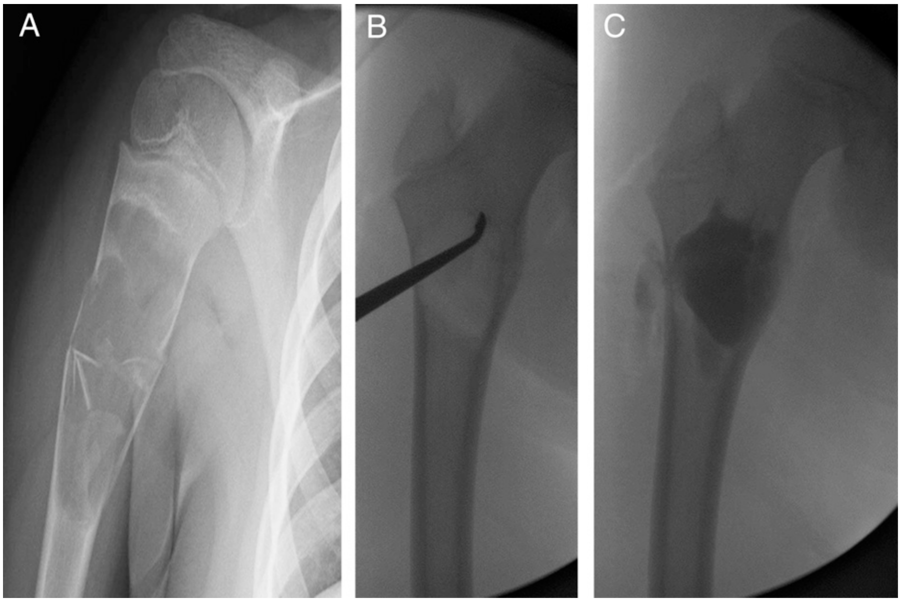

Figure 3. A. "Fallen leaf" sign. B. Percutaneous curettage. C. Grafting with synthetic bone graft substitute.

periodic observation is all that is needed. If the patient is asymptomatic, restriction of activities may not be necessary.

Because of the potential for complications after hip fractures, lesions in this location are usually treated surgically regardless of their size or symptoms.

The preoperative evaluation of patients with simple bone cysts rarely requires more than good-quality radiographs of the lesion. If the diagnosis is equivocal, a bone scan will verify the presence or absence of other abnormal areas. Computed tomography may be helpful in differentiating simple bone cysts from other lesions, such as ABCs or fibrous dysplasia. Findings on MRI of double-density fluid levels and septations associated with low signal on T1-weighted images and high signal on T2-weighted images strongly suggest the presence of an ABC rather than a simple bone cyst. (17)

Several treatment options are available for UBCs. Treatment modalities include injection of corticosteroids into the cyst, injection of autologous bone marrow, multiple drilling and drainage of the cavity, and curettage of the membranous wall followed by bone grafting. A relatively high recurrence rate has been historically associated with all treatment options of simple bone cysts.

Most authors now agree that cyst decompression is essential for adequate healing. A minimally invasive technique with cyst decompression, percutaneous curettage, and use of synthetic bone graft substitutes (injectable calcium sulfate and calcium phosphate) is the preferred treatment at most institutions. (18) (Fig 3B and C)

Medical Therapies

The theoretical use of bisphosphonates and botulinum toxin type A injections for the management of UBCs has been investigated in some basic science research. (19)(20) However, there are no established or recommended medical noninterventional treatments for this condition. (9)

ANEURYSMAL BONE CYSTS

Incidence

An ABC is a solitary, expansile, radiolucent lesion usually located in the metaphyseal region of the long bones. Fortunately, ABCs are seen much less often than simple bone cysts, and they represent only 1% of all primary bone tumors sampled for biopsy; the annual incidence of primary ABCs approximates 0.1 per 10^9 individuals. (21)(22) Nearly 70% of affected patients are aged 5 to 20 years, and approximately half of these cysts occur in the second decade of life, although the lesion has been reported in infants. No sex predilection is reported. (21)

Aneurysmal bone cysts can be located throughout the skeleton, and the most common sites are the femur, tibia, spine, humerus, pelvis, and fibula, with approximately half of reported cases occurring in the long bones of the extremities. (21)(23) Although they usually arise in the metaphyseal region of the bone, ABCs may sometimes cross the physis into the epiphysis or extend into the diaphysis. (24)

Approximately 20% of ABCs involve the spine. They may occur anywhere between the axis (25)(26)(27) and the sacrum (28) and can cause spinal cord compression or spinal deformity. (29)(30) In the vertebra itself, the cyst may be found in the body, pedicles, lamina, and spinous process (Fig 4). Involvement of 2 or more adjacent vertebrae is not uncommon. Aneurysmal bone cysts may also occur in the maxilla, frontal sinus, orbit, zygoma, ethmoid, temporal bone, mandible, sternum, clavicle, hands, and feet. (31)

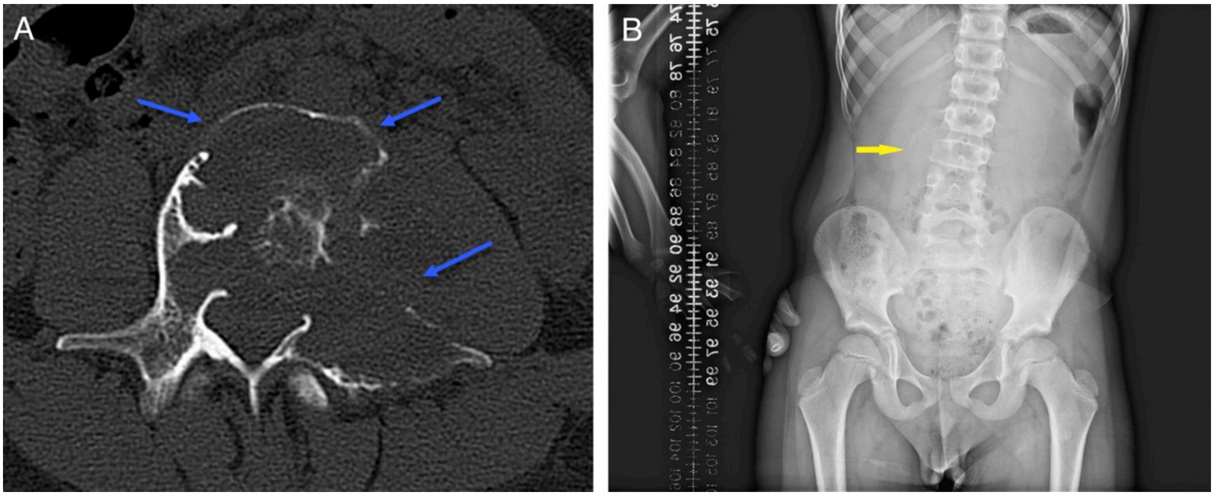

Figure 4. A. Axial computed tomographic scan of a large aneurysmal bone cyst (blue arrows) in the cervical spine. Courtesy of Frank Gaillard (http://radiopaedia.org/articles/aneurysmal-bone-cyst). B. Lumbar spine anteroposterior radiograph showing a lytic lesion of right L3 (winking owl sign) (yellow arrow).

Etiology

The etiology of ABCs is not precisely known. The literature suggests that ABCs represent either a primary neoplastic condition or a secondary response (arteriovenous malformation) due to the local destructive effects of an underlying primary tumor. (32)

Recently, genetic research has shed some light on the etiology of ABC, leading some to believe that ABC is a true neoplasm rather than a reactive process. (33) Histopathologic studies have reported that gene rearrangements localized to t(16;17) and involving chromosome segments 7q, 16p, and 17p11-13 confirm a true neoplastic etiology. (31)(34) Others have shown that upregulation of proteases may ultimately lead to tumorigenesis. (28) Immunohistochemical and in situ hybridization studies found insulinlike growth factor I, or messenger RNA coding for this growth factor, primarily localized in multinucleate giant cells in all of the ABCs sampled. (35) Insignificant levels of expression were found in normal human bone tissue. These findings support the theory that genetic factors may play a significant role in the development of primary ABC.

Clinical Features

The clinical presentation of an ABC includes localized pain for several weeks' duration, tenderness, and, if the ABC occurs in an extremity, swelling. As with most benign bony malignancies, secondary symptoms such as fever, weight loss, malaise, nausea, or vomiting are not common. When an ABC involves the spine, progressive enlargement may compress the spinal cord or nerve roots and, similar to any space-occupying lesion, result in neurologic deficits such as motor weakness, sensory disturbance, and loss of bowel or bladder control. Spinal involvement, therefore, mandates urgent intervention.

Radiographic Findings

Aneurysmal bone cysts have a classic appearance of a radiolucent cystic lesion in the metaphyseal portion of the bone. Originally described as a periosteal "blowout" lesion, (36) the lesion is destructive and may expand beyond the surrounding cortical bone. The mass may elevate the periosteum, but it typically remains contained by a thin shell of cortex. Typically, ABCs are eccentric but may also be central or subperiosteal (Fig 5). Lesions in the epiphysis are atypical and should raise suspicion of secondary changes caused by a neoplastic process. (37) Occasionally, computed tomography is used preoperatively to better define the full extent of the lesion, especially with spinal lesions. An MRI with contrast classically demonstrates internal septations that may contain characteristic fluid-fluid levels, caused by layering of blood products in cystic areas of the lesion (Fig 6).

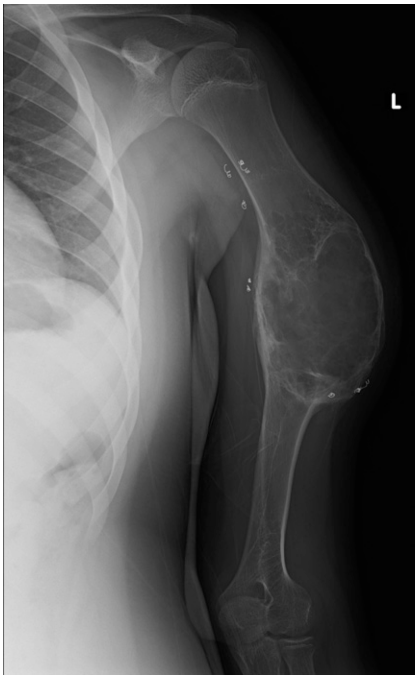

Figure 5. Radiograph of a 14-year-old boy with a large aneurysmal bone cyst in the left humerus (clips seen are from previous vessel ligation).

Differential Diagnosis

The differential diagnosis includes but is not limited to enchondroma, UBC, and lesions from which an ABC may develop; atypical osteosarcoma and telangiectatic osteosarcoma; chondroblastoma; fibrous dysplasia; and giant cell tumor. These lesions may mimic ABCs radiologically or present with fluid levels similar to ABCs on MRI. Most

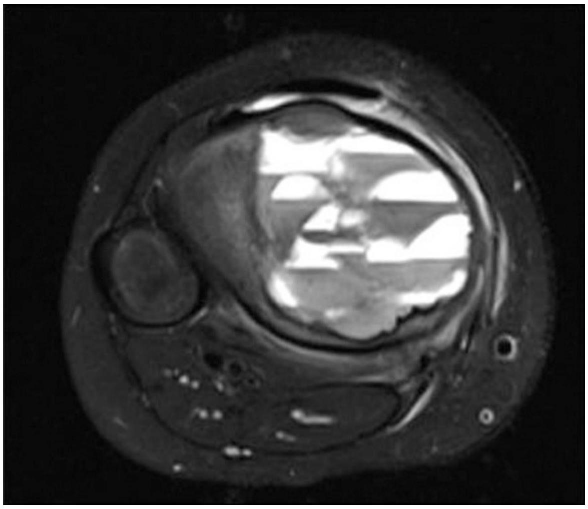

Figure 6. Characteristic fluid-fluid levels seen on this T2-weighted fat-saturated axial magnetic resonance image of an aneurysmal bone cyst. Courtesy of Frank Gaillard (http://radiopaedia.org/articles/aneurysmal-bone-cyst).

notably, ABCs are more prominently expansile with a thin cortical shell compared with the other compared lesions.

Treatment

Although spontaneous healing of ABCs has been reported, (38) it is uncommon. Thus, expectant management should be considered only when the diagnosis has been confirmed and the lesion is in a location and currently at a stage that does not pose a risk of fracture or further destruction. Quite often, when the diagnosis of ABC is made, prompt active treatment is recommended.

Presently, curettage and bone grafting, with or without adjuvant therapy, is the accepted method for the management of ABC. Adjuvant therapy may include but is not limited to phenol, liquid nitrogen, peroxide, and argon beam coagulation. Cryotherapy has also been found to reduce the recurrence rate of ABC. A noninvasive management method, sclerotherapy, is based on the theory that ABCs originate as a vascular malformation and can possibly heal if the hemodynamic disturbance were controlled. Recently, radionuclide ablation has been proposed for the management of ABCs. This method has been used successfully to manage other diseases, such as rheumatic synovitis and recurrent hemarthroses associated with hemophilia. (33) Selective arterial embolization is useful for the management of ABCs in areas of limited access, but it is mostly used preoperatively to interrupt blood flow to the lesion. "En bloc resection has been associated with the lowest rate of recurrence after initial treatment compared with other management methods. Unfortunately, this technique is not always feasible due to the location of the lesion and its proximity to other vital structures." (33)

Summary

Unicameral bone cysts (UBCs) and aneurysmal bone cysts (ABCs) have significant differences; however, for the general pediatrician, there are a few key points to ensure proper care and treatment of these bony lesions:

- A UBC is also known as a simple bone cyst and is usually found in patients younger than 20 years, most commonly in the proximal humerus and femur.
- A UBC is a central lytic lesion in the metaphysis and typically resolves with skeletal maturity. However, close follow-up is necessary while the patient is growing due to risk of fracture and growth disturbance.
- Any UBCs that are adjacent to the physis, causing continued pain, or have an associated fracture should be referred to an orthopedic surgeon for monitoring of deformity, surgical intervention or immobilization if fracture is present.
- The ABCs are also found in patients younger than 20 years, most commonly in the metaphysis of long bones.
- An ABC is more expansive than a UBC and may be wider than the width of the physis. On radiographs, ABCs are also eccentric and lytic, with bony septae or a "bubbly" appearance.
- An ABC may have an associated pathologic fracture, and the patient should be referred to an orthopedist. The patient typically will be immobilized until healed, at which time the ABC will be treated operatively.
- It is imperative to always perform a good physical examination because soft tissue swelling may occur in ABCs, but soft tissue edema and local tenderness are more common for the most alarming lesion on the differential diagnosis, the telangiectatic osteosarcoma. Any concerns or increased or continued pain should be referred for biopsy.

For ABCs and UBCs, morbidity is a possibility with any treatment option. There are risks associated with surgical intervention, and there are risks and consequences of pathologic fracture that may occur without intervention. When injection or surgical intervention is warranted, studies that support different management options are lacking evidence quality. There are few to no level A randomized controlled trials. (39) The remaining body of literature on level of evidence remains low. Based on some research evidence as well as consensus, most authors now agree that cyst decompression is essential for adequate healing. A minimally invasive technique with cyst decompression, percutaneous curettage, and use of synthetic bone graft substitutes (injectable calcium sulfate and calcium phosphate) is the preferred treatment at most institutions.

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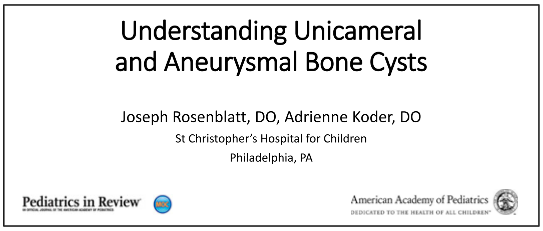

Understanding Unicameral and Aneurysmal Bone Cysts

Joseph Rosenblatt, DO, Adrienne Koder, DO

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1. A 5-year-old previously healthy girl is seen in the clinic for a persistent cough for the past 2 weeks. On physical examination she is noted to have a low-grade fever. Pulse oximetry is 95% on room air. Crackles are heard over the right lung base. A chest radiograph shows a right middle lobe pneumonia. In addition, the radiologist reports a small solitary bone cyst in the left upper humerus. The treating physician discusses the findings with the parents and inquires whether the patient has any left upper arm pain. The parents deny that their daughter has any pain. Findings from examination of the left arm are normal. In addition to prescribing oral antibiotics for the pneumonia, which of the following is the most appropriate next step in the management of this patient's bone cyst?
   A. Bone biopsy from the left upper humerus.
   B. Bone scan.
   C. Magnetic resonance imaging (MRI) of the left arm.
   D. Observation and monitoring for symptoms or pain.
   E. Skeletal survey.
2. A 7-year-old boy is brought to your office after sustaining a fall while running. He is now limping on the right side. On physical examination there is mild swelling on his right tibia just below the knee joint. The patient is unable to bear weight on his right leg. Radiographs show a right tibial nondisplaced fracture and a bone cyst. The patient was seen by orthopedics, and a posterior splint was placed to his right lower extremity. Which of the following is the most appropriate next step in the management of the bone cyst?
   A. Cyst curettage after the fracture is healed.
   B. Observation and reassurance.
   C. Open pin fixation of the fracture with bone graft of the cyst.
   D. Removal of the cyst only if no evidence of fracture healing in 6 weeks.
   E. Weekly corticosteroid injections in the fracture plane around the cyst during the fracture healing phase.
3. You practice in a remote town where you see a 17-year-old young man complaining of occasional left upper arm pain when he lifts heavy objects. On physical examination there is no obvious deformity, swelling, or redness. Radiographs of the extremity reveal a radiolucent cystic structure with a thick cortical rim in the metaphyseal region of the left proximal humerus. The patient is diagnosed as having a solitary left humeral bone cyst. Which of the following is the next best step in the management of this patient?
   A. Activity restriction.
   B. Follow-up radiography in 2 months.
   C. Immobilization of the left arm in a sling for 6 weeks.
   D. Orthopedic referral for cyst curettage.
   E. Periodic observation.
4. An 8-year-old boy presents to the clinic with progressively increasing pain in the right thigh area with some swelling. The family denies any trauma, and the patient occasionally limps. There is no history of fevers or weight loss. Bilateral hip and right femur radiographs show a cystic lesion in the metaphysis of the right femur. An MRI of the right femur with contrast shows a cyst with a thin cortical shell with internal septation and fluid levels. Which of the following is the most likely diagnosis in this patient?
   A. Aneurysmal bone cyst.
   B. Atypical osteosarcoma.
   C. Enchondroma.
   D. Ewing sarcoma.
   E. Giant cell tumor.

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5. The patient from the vignette in question 4 is referred to orthopedics for further management. The family is worried about the treatment and the potential for recurrence. Which of the following is the most appropriate and effective next step in the management of this patient?
   A. Curettage, bone grafting, and cryotherapy as adjuvant therapy.
   B. No weight bearing for 3 weeks.
   C. Observation and reassurance.
   D. Prescribe nonsteroidal anti-inflammatory drugs and follow up in 2 weeks with repeated MRI to assess involution.
   E. Weekly corticosteroid injections to the right hip.

Understanding Unicameral and Aneurysmal Bone Cysts

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Pediatrics in Review 2019;40;51
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Congestive Heart Failure in Children

Jack F. Price, MD*

**Department of Pediatrics, Baylor College of Medicine, and Advanced Heart Failure Unit, Texas Children's Hospital, Houston, TX*

Education Gaps

1. The signs and symptoms of heart failure in children are frequently mistaken for other more common childhood illnesses.
2. Standard-of-care medications are commonly underprescribed in children who are discharged after hospitalization for heart failure. (1)

Objectives

After completing this article, readers should be able to:

1. Recognize the signs and symptoms of heart failure in children of various ages.
2. Identify the causes of heart failure in children of various ages.
3. Plan the initial diagnostic evaluation of heart failure in children.
4. Plan the initial treatment of heart failure in children.

Abstract

Congestive heart failure is a final common clinical pathway for several diseases in childhood, such as familial cardiomyopathy, viral myocarditis, inborn errors of metabolism, and autoimmune disorders. Early identification and treatment can reduce symptom severity and may affect outcomes. In this review, the clinical characteristics of pediatric heart failure are described, and the initial diagnostic evaluation is outlined. Evidence-based heart failure treatment strategies at various clinical stages are discussed in detail, including the management of acute decompensated heart failure.

INTRODUCTION

A good definition of congestive heart failure (HF) is elusive and has changed over time with our understanding of the pathophysiology of the failing heart. This is especially true in pediatrics because the etiology and symptoms of HF may differ by age group. Dr Arnold Katz has proposed a popular definition of HF in adults that acknowledges a clinical pattern of myocardial disease and a neurohormonal paradigm responsible for its progression: "a clinical syndrome in which heart disease reduces cardiac output, increases venous pressures, and is accompanied

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ABBREVIATIONS

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
AHA	American Heart Association
ALCAPA	anomalous left coronary artery from the pulmonary artery
BNP	B-type natriuretic peptide
CCS	Canadian Cardiovascular Society
DCM	dilated cardiomyopathy
HF	heart failure
ISHLT	International Society for Heart and Lung Transplantation
MCS	mechanical circulatory support

by molecular abnormalities that cause progressive deterioration of the failing heart and premature myocardial cell death." (2) Most pediatric HF specialists would agree that pulmonary overcirculation that results from a large left-to-right intracardiac shunt (eg, ventricular septal defect) is not HF. For the purposes of this review, the term *heart failure* is limited to children whose signs and symptoms are attributable to ventricular dysfunction.

CLASSIFICATION OF HF

The American College of Cardiology (ACC) and the American Heart Association (AHA) staging classification of HF is a useful tool for categorizing patients across populations. (3) The staging system emphasizes the onset and progression of the disease, unlike the New York Heart Association functional classification system, which emphasizes exercise capacity. (4) The International Society for Heart and Lung Transplantation (ISHLT) published guidelines and recommendations for the evaluation and treatment of HF in children in 2004 and proposed a staging classification (Table 1). (5)

ETIOLOGY OF NEW-ONSET HF

The etiology of new-onset HF varies by age (Table 2). In newborns and infants, structural heart disease commonly leads to ventricular dysfunction and HF. Congenital abnormalities such as anomalous left coronary artery from the pulmonary artery (ALCAPA), critical aortic stenosis, coarctation of the aorta, and single-ventricle congenital heart disease are frequently associated with ventricular chamber enlargement, abnormal ventricular systolic and/or diastolic function, and signs of HF. Although rare, inborn errors of metabolism may also cause HF in infancy. Diseases such as fatty acid oxidation disorder and other mitochondrial disorders may lead to hypertrophic or dilated forms of cardiomyopathy with impaired ventricular function.

Dilated cardiomyopathy (DCM) is the most common myopathic process leading to HF in children. The annual incidence of DCM in US children is 0.57 cases per 100,000. (6) In children, DCM may be caused by genetic mutations, autoimmune diseases, infectious diseases, drug exposures, and endocrine disorders (Table 3). Familial forms of DCM occur in approximately 20% to 50% of affected children. The most common inheritance pattern of DCM is autosomal dominant, although X-linked and autosomal recessive patterns also occur. Spontaneous, or de novo, mutations have been described as well.

The most common cause of acquired DCM in children is myocarditis. Acute myocarditis is usually attributed to a virus or other infectious agent. Viruses such as enterovirus, parvovirus, and adenovirus are frequently implicated. Infection with human immunodeficiency virus may also lead to HF. The prevalence of cardiac involvement is high among human immunodeficiency virus–positive children and includes ventricular chamber enlargement (DCM), increased ventricular mass, arrhythmias, and pericardial effusion. Noninfectious agents, such as drugs or toxins, can also cause myocarditis and a dilated form of cardiomyopathy.

Beyond infancy, other causes of HF are encountered. Kawasaki disease may cause large coronary artery aneurysms that can lead to vascular thrombosis and myocardial ischemia with ventricular dysfunction early in the disease

TABLE 1. Proposed HF Classification for Infants and Children

STAGE	DEFINITION	EXAMPLES
A	Patients with increased risk of developing HF but who have normal cardiac function and no evidence of cardiac chamber volume overload.	Previous exposure to cardiotoxic agents, family history of heritable cardiomyopathy, univentricular heart, congenitally corrected transposition of the great arteries.
B	Patients with abnormal cardiac morphology or cardiac function, with no symptoms of HF, past or present.	Aortic insufficiency with LV enlargement, history of anthracycline with decreased LV systolic function.
C	Patients with underlying structural or functional heart disease, and past or current symptoms of HF.	Dilated cardiomyopathy with chronic HF due to decreased LV systolic function.
D	Patients with end-stage HF requiring continuous infusion of inotropic agents, mechanical circulatory support, cardiac transplant, or hospice care.	Acute decompensated HF due to viral myocarditis.

HF=heart failure, LV=left ventricular.

From Rosenthal D, Chrisant MR, Edens E, et al. International Society for Heart and Lung Transplantation: practice guidelines for management of heart failure in children. J Heart Lung Transplant. *2004;23(12):1313.*

TABLE 2. Etiology of New-Onset Heart Failure by Age

Newborns and infants	Acute viral myocarditis Idiopathic dilated cardiomyopathy Familial cardiomyopathy Anomalous left coronary artery origin from the pulmonary artery Tachycardia-induced cardiomyopathy Inborn error of metabolism Hypertrophic cardiomyopathy Coarctation of the aorta Critical aortic stenosis Single-ventricle congenital heart disease
Age 2-5 y	Acute viral myocarditis Idiopathic dilated cardiomyopathy Familial cardiomyopathy Single-ventricle congenital heart disease Tachycardia-induced cardiomyopathy Kawasaki disease
Age >5 y	Acute viral myocarditis Idiopathic dilated cardiomyopathy Familial cardiomyopathy Tachycardia-induced cardiomyopathy Single-ventricle congenital heart disease Rheumatic heart disease Anemia Hypothyroidism Systemic lupus erythematosus

process. Over several years, the coronary arteries may develop stenoses and occlusion. Autoimmune disorders, such as systemic lupus erythematosus and rheumatic heart disease, may occur in older children and adolescents. These disorders cause myocardial inflammation with vascular stenosis, valvulitis, myocardial fibrosis, and ventricular dysfunction.

Neuromuscular disorders such as Duchenne and Becker muscular dystrophies are also associated with DCM and HF in children. Boys with Duchenne muscular dystrophy commonly develop DCM, usually in puberty or early adolescence. Although they are living longer due to advances in respiratory therapies, death from HF and sudden death is increasing in frequency.

Abnormal and sustained heart rhythms, usually tachyarrhythmias, may also lead to DCM and HF. Atrial ectopic tachycardia is the most common cause of tachycardia-induced cardiomyopathy. Fortunately, cardiac function usually normalizes within a few months of rhythm control with either medication or an ablation procedure.

CLINICAL FEATURES OF HF

Children with HF caused by DCM may present with clinical features that mimic many other diseases of childhood, such as bronchitis and gastrointestinal disease. Most children with HF complain of fatigue or lack of energy, labored breathing (either at rest or with exertion), abdominal pain, and nausea or vomiting (Table 4). Other symptoms may include chest pain and wheezing.

In children, the clinical signs of HF may not be obvious on physical examination. (7) Resting tachycardia and tachypnea are commonly present in all ages. Blood pressure, however, is usually normal except in patients with cardiogenic shock or impending shock. Signs of fluid overload, such as hepatomegaly and a gallop rhythm, are common in children; however, other findings of congestion, such as edema of the lower extremities, abdominal ascites, rales, and jugular venous distention, are identified less frequently. Signs of poor perfusion may be present, including delayed capillary refill and cool distal extremities. A blowing holosystolic murmur at the apex may be appreciated in patients with a dilated left ventricular chamber and an incompetent mitral valve.

CLINICAL EVALUATION OF HF

Diagnostic tools such as chest radiography and electrocardiography can help determine whether a child's signs or symptoms are attributable to HF. On chest radiography, the cardiac silhouette is usually enlarged (Figs 1 and 2). Severe mitral regurgitation can lead to left atrial enlargement, which may be appreciated on a lateral projection. Children with HF frequently have normal lung markings on chest radiographs. Increased pulmonary vascular markings, alveolar edema, and pleural effusions may be seen on radiographs, but the absence of these findings does not rule out HF.

The electrocardiogram commonly demonstrates nonspecific abnormalities such as ventricular hypertrophy by voltage criteria and ST-segment or T-wave changes. Sometimes it will reveal electrical conduction disturbances, especially in patients with advanced disease. Rhythm disturbances are also common in patients with HF and may include supraventricular tachycardia, atrial fibrillation/flutter, atrioventricular block, and ventricular tachycardia.

Laboratory biomarkers of heart failure may help establish a diagnosis. B-type natriuretic peptide (BNP) and N-terminal proBNP concentrations are almost always elevated in children with HF and may portend a poor prognosis in the outpatient setting. Serum electrolytes and markers of kidney function may be abnormal, especially in patients with decompensated HF. Hyponatremia is frequently identified in patients with advanced disease and is associated with

TABLE 3. **Etiology of Dilated Cardiomyopathy in Childhood**

FACTOR	EXAMPLES
Genetic mutations	Lamin A-C, myosin binding protein-C, tropinin I, taffazin (Barth syndrome), dystrophin, LAMP2 (Danon disease), mitochondrial disorders, limb-girdle dystrophy, titin, desmin
Myocarditis	Enteroviruses, parvovirus, adenovirus, influenza, Epstein-Barr virus, human immunodeficiency virus, cytomegalovirus, varicella, mumps, Giant cell disease, Lyme disease, mycoplasma
Ischemia	Anomalous origin of left coronary artery from pulmonary artery, Kawasaki disease with coronary aneurysms
Metabolic disorders	Disorders of fatty acid oxidation, glycogen storage disorders (eg, Pompe), carnitine deficiency
Structural heart disease	Valvular disease, congenital heart disease
Endocrine disorders	Hypothyroidism, parathyroid disease, pheochromocytoma
Hematologic disorders	Iron deficiency, sickle cell anemia, hemochromacytosis, thalassemia
Autoimmune/collagen vascular diseases	Systemic lupus erythematosus, dermatomyositis, rheumatic heart disease
Toxins	Anthracycline, radiation, cyclophosphamide

worse outcomes in hospitalized patients. (8) Kidney function should be evaluated and monitored in children with HF because low cardiac output and venous congestion may lead to kidney injury and further progression of the disease and exacerbation of symptoms.

An echocardiogram should be performed in any child with suspected ventricular dysfunction or HF. It can reveal important information about ventricular chamber size and systolic/diastolic function. In children younger than 1 year with newly diagnosed DCM with HF, it is compulsory to determine the origins of the coronary arteries to rule out ALCAPA. In left ventricular noncompaction cardiomyopathy, the myocardium will appear heavily trabeculated, with fingerlike projections and recesses along the left ventricular apex and free wall. Left atrial enlargement is frequently seen on echocardiograms in the presence of severe mitral regurgitation. Bi-atrial enlargement should raise suspicion for restrictive cardiomyopathy.

TREATMENT OF HF

Only 1 large randomized controlled trial has ever been conducted to assess the efficacy and safety of oral HF therapy in children. (9) Most of our understanding of the management of HF comes from studies performed in adults with HF resulting from ischemic heart disease. Until more therapies are studied in children, the pediatrician must rely on evidence from large trials in adults, familiarizing oneself with the societal guidelines and cautiously applying those recommendations to the pediatric HF population.

In 1995, the ACC and the AHA formed a task force to recommend practice guidelines for the evaluation and management of HF in adults. The guidelines were reassessed and expanded in 2013 with collaboration from the ISHLT, the American College of Chest Physicians, and the Heart Rhythm Society. (3) An updated version has been endorsed

TABLE 4. **Clinical Features of Decompensated Pediatric Heart Failure**

AGE	SIGNS OF HEART FAILURE	SYMPTOMS OF HEART FAILURE[a]
Newborns, infants, and toddlers	Tachycardia, tachypnea, diaphoresis, grunting, nasal flaring, crackles, wheezing, gallop rhythm, displaced point of maximal impulse, pallor, hepatomegaly, poor perfusion	Poor weight gain, decreased oral intake, increased work of breathing, fussiness, diaphoresis
Age ≥5 y	Tachycardia, tachypnea, peripheral edema, jugular venous distention, wheezing, gallop, hepatomegaly	Abdominal pain, nausea and vomiting, dyspnea at rest or with exercise, orthopnea, fatigue, poor appetite, cough

[a] *As reported by a parent or guardian in the youngest patients.*

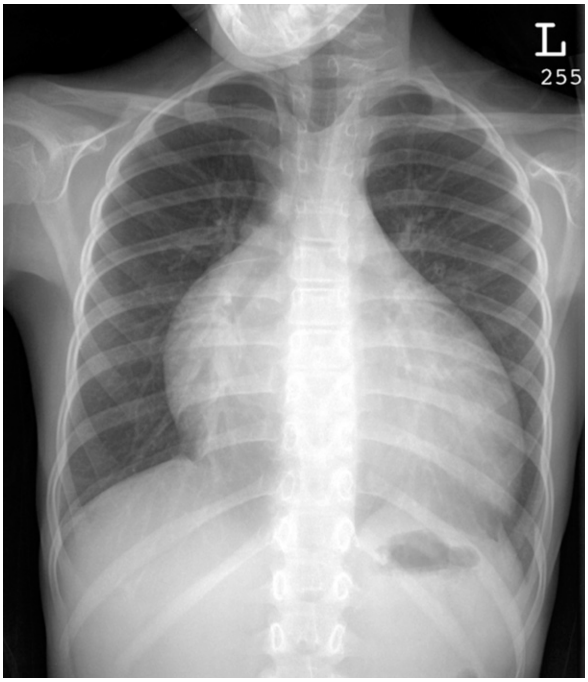

Figure 1. Anteroposterior chest radiograph of a child with dilated cardiomyopathy and new-onset heart failure. Marked cardiomegaly is present, but there is no evidence of pulmonary vascular congestion and only trace pleural effusion on the left.

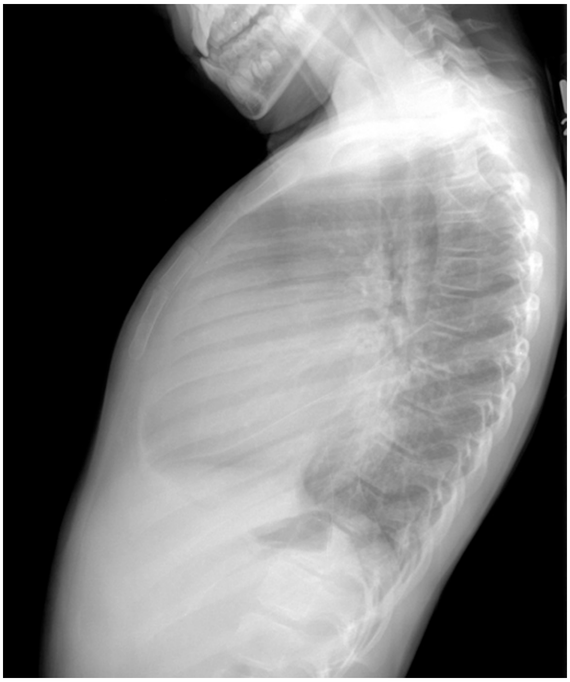

Figure 2. Lateral chest radiograph.

by the Heart Failure Society of America. (10) The Canadian Cardiovascular Society (CCS) and the ISHLT have both published guidelines for the evaluation and management of HF in children, relying heavily on published data in adults to make recommendations. (11)(12) See Fig 3 for graduated medical therapies based on HF clinical stage.

Stage A

In stage A, no particular HF medications are recommended; however, regular clinical surveillance and monitoring are important for patients who are at high risk for HF. For example, patients with cancer who have received cardiotoxic chemotherapeutic agents (eg, anthracyclines) should be considered for annual screening with echocardiography. Similarly, patients with chronic kidney disease, especially those who require dialysis, are at risk for ventricular dysfunction and HF and may benefit from routine cardiac follow-up.

Stage B

The ACC Foundation/AHA HF guidelines recommend the use of angiotensin-converting enzyme (ACE) inhibitors in asymptomatic adults with impaired systolic function to prevent the development of symptomatic HF. Inhibition of the ACE has been widely studied in adults with congestive HF. Landmark investigations have demonstrated improved functional capacity, fewer hospitalizations, and decreased mortality in adult patients with HF. There is strong evidence for the benefits of ACE inhibition in both ischemic and nonischemic forms of heart disease and even in asymptomatic patients. (13)(14)(15)(16)(17)(18)(19)

The Studies of Left Ventricular Dysfunction evaluated the impact of enalapril on mortality in asymptomatic adults with decreased left ventricular systolic function and in patients with symptomatic HF. (18)(19) Patients with asymptomatic left ventricular dysfunction were randomized to either enalapril or placebo and were followed for a mean of just over 3 years. No reduction in mortality was observed; however, when patients who died were combined with those who progressed to symptomatic HF, a risk reduction of 29% was identified in those treated with enalapril. In addition, patients treated with enalapril were less likely to require hospitalization for HF.

The evidence is less robust for children, however, and we understand little about the efficacy of ACE inhibition in children with myocardial dysfunction. Retrospective data have shown a survival benefit for children with DCM, but these findings have not been duplicated in subsequent studies. (20)(21) Enalapril may reduce left ventricular wall stress and improve function in children treated with chemotherapeutic agents.

The CCS give a strong recommendation for the use of ACE inhibitors in children with HF. It also recommends

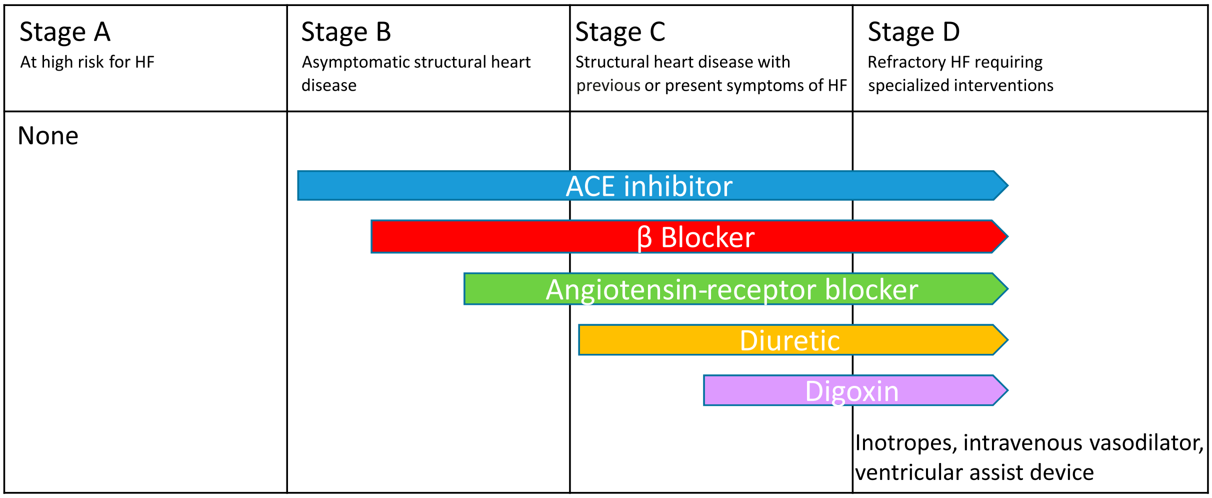
Stage A
At high risk for HF
Stage B
Asymptomatic structural heart disease
Stage C
Structural heart disease with previous or present symptoms of HF
Stage D
Refractory HF requiring specialized interventions
None
ACE inhibitor
β Blocker
Angiotensin-receptor blocker
Diuretic
Digoxin
Inotropes, intravenous vasodilator, ventricular assist device

Figure 3. Medical therapy for heart failure (HF) by stage. Angiotensin-converting enzyme (ACE) inhibitors and β-blockers may by initiated in asymptomatic individuals with ventricular dysfunction at a low dose and uptitrated to the target dosage based on tolerance of the medication. (Modified with permission from Kantor PF, Lougheed J, Dancea A, et al; Children's Heart Failure Study Group. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. *Can J Cardiol*. 2013;29(12):1535–1552.)

caution when initiating and uptitrating ACE inhibitors during the first 4 months after birth due to the risk of renal dysfunction. (11) Captopril is more often prescribed to newborns and infants, whereas longer-acting lisinopril and enalapril are prescribed to older children. See Table 5 for suggested target dosages.

β-Blockers are also recommended by the ACC Foundation/AHA in asymptomatic patients with ventricular systolic dysfunction. (3) Several years ago, β-blocker therapy in patients with left ventricular dysfunction was viewed with skepticism. It has since become the established standard of care and is very frequently used in conjunction with an ACE inhibitor. Several decades ago, numerous small trials signaled potential hemodynamic and clinical benefits of β-blocker treatment. Subsequent large-scale studies have demonstrated the safety and efficacy of β-blocker use for treating symptoms and reducing morbidity and mortality. (22)(23)(24)(25)(26)(27) (28)(29)(30)(31) Accordingly, β-blockers are now a mainstay of HF therapy in adult patients.

Among the β-blockers, carvedilol is the most thoroughly investigated and prescribed. It attenuates the effects of high

TABLE 5. **Heart Failure Medication Target Dosing**

β-BLOCKERS	ACE INHIBITORS	DIURETIC/ALDOSTERONE ANTAGONISTS
Carvedilol	**Captopril**	**Furosemide**
Infants and young children: 0.8–1 mg/kg per day	Infants: 1–4 mg/kg per day	Infants and young children: 1–2 mg/kg per dose every 6–24 h
Children (<50 kg): 25 mg/day	Children (>50 kg): 150 mg/day	Children (>50 kg): 20–80 mg/day
Children (>50 kg): 50 mg/day		
Metoprolol	**Enalapril**	**Spironolactone**
Infants and young children: 2 mg/kg per day	Infants and young children: 0.4–0.5 mg/kg per day	Infants and young children: 1–3.3 mg/kg per day divided doses every 6–24 h
Children (<50 kg): 100 mg/day	Children (<50 kg): 10 mg/day	May increase to 5–6 mg/kg per day
Children (>50 kg): 200 mg/day	Children (>50 kg): 20 mg/day	Maximum dose: 100 mg/day

ACE=angiotensin-converting enzyme.
From the Texas Children's Hospital Cardiomyopathy and Heart Failure Service, Houston, TX.

circulating concentrations of norepinephrine and upregulates β-receptor density in HF, leading to improved chamber remodeling and function. In one study of asymptomatic patients with stage B HF and low ejection fraction, administration of carvedilol resulted in a 31% reduction in the risk of deleterious long-term outcomes. (32) The ISHLT guidelines state that "following adult heart failure guidelines, it is reasonable to consider β-blockers in asymptomatic children with systemic LV [left ventricular] systolic dysfunction." Therapy should start at a small dose and slowly uptitrate. The CCS recommends starting at a dose of 0.05 mg/kg every 12 hours and uptitrating to the target dose over several weeks.

Stage C

Patients with stage C HF have "functional heart disease with prior or current symptoms of heart failure." (3) In this population, the goals of therapy are to provide symptomatic relief and limit progression of the disease. Both ACE inhibitors and β-blockers are recommended in children with stage C HF. Generally, if these medications are being introduced at this stage, they are added sequentially, and ACE inhibitors are started first.

The Cooperative North Scandinavian Enalapril Survival Study was a randomized study of adults with severe HF who received either enalapril or placebo. (17) Mortality was reduced by 31% at 1 year in patients who received enalapril compared with patients who received placebo.

β-Blockers reduce morbidity and mortality in patients with chronic HF. A study evaluating the efficacy of carvedilol in patients with chronic HF (26) found a beneficial effect of carvedilol on survival. The mortality risk in patients treated with carvedilol was significantly lower compared with placebo (3.2% carvedilol vs 7.8% placebo; $P < .001$). In addition, there was a 27% reduction in the risk of cardiac hospitalization (14.1% vs 19.6%; $P = .036$).

Only 1 multicenter, randomized study has been performed of the effects of β-blockers in children with HF. (9) Symptomatic children and adolescents were randomized to receive either carvedilol or placebo and were treated for 6 months. The investigators found no significant improvement in clinical outcomes in children who received carvedilol compared with placebo. This may be due to the fact that the study was underpowered or that 56% of patients who received placebo had significant clinical improvements.

Despite the paucity of controlled studies in children, the consensus opinion among HF specialists is that ACE inhibitors and β-blockers should be prescribed to eligible pediatric patients with HF. It is safe and advisable to prescribe these medications before discharge in hospitalized patients. The prescription rate in discharged children is quite low, however. Moffett and Price (1) found wide variation in the use of ACE inhibitors and β-blockers in children at hospital discharge, with most centers prescribing at rates less than 50%. Furthermore, only 40% to 60% of eligible patients were prescribed these medications at hospital discharge.

In patients who exhibit signs or symptoms of congestion due to fluid overload, diuretics can be administered for symptomatic relief. Loop diuretics, such as furosemide, are the preferred first-line agents for most children with HF. Diuretics can reduce body weight and edema in patients with HF with mild-to-moderate symptoms and may improve stroke volume and ventricular performance in certain patients. The effects of diuretics on mortality are not known; however, a Cochrane analysis of several small studies in adult patients with chronic HF showed that conventional diuretics may decrease the incidence of death and worsening HF. (33)

Aldosterone antagonists are relatively weak diuretics but have other features (antifibrotic) that benefit patients with HF. There is strong evidence in adults that aldosterone antagonists reduce mortality and alleviate HF symptoms. In the Randomized Aldactone Evaluation Study of adults with severe HF, randomization to receive spironolactone was associated with a 30% reduction in the risk of death and a decreased frequency of hospitalization for worsening HF. (34) In addition, HF symptoms significantly improved in patients treated with spironolactone. Spironolactone is the most common aldosterone antagonist used in children. It is reasonable to consider its use in children with ventricular dysfunction and mild-to-moderate symptoms. Spironolactone is generally prescribed after an ACE inhibitor and a β-blocker have been initiated and uptitrated to target dosing. Renal function and serum potassium should be monitored closely, especially if co-administered with an ACE inhibitor. Spironolactone should be avoided in patients with a creatinine clearance less than 30 mL/min/1.72 m^2 (0.50 mL/s/m^2).

Historically, digoxin was prescribed commonly in children with HF. This therapy seems sensible given the potential beneficial effects of digoxin, including increased inotropic response, attenuated neurohormonal response, and enhanced control of heart rate in adult patients with atrial fibrillation. Digoxin seems to ameliorate symptoms of advanced HF and improve quality of life, but there are no data showing improved survival. It may be prescribed in children with symptomatic HF attributable to ventricular dysfunction but at a low dose (5–10 μg/kg per day). (35) Serum digoxin concentrations should be measured in follow-up with a goal value of 0.5 to 0.8 ng/mL (0.64–1.02 nmol/L).

Stage D

In stage D, patients have developed symptomatic HF that is refractory to optimized oral therapies, and they frequently require inpatient treatments. This stage may be characterized by frequent hospitalizations for fluid overload or low cardiac output and by development of comorbidities such as anemia, renal impairment, and hyponatremia. For some patients, their disease may progress to end-stage, at which point long-term survival requires cardiac transplant and/or mechanical circulatory support (MCS).

Diuretics, Fluid Restriction, and Nutrition

Intravenous loop diuretics should be considered first-line therapy for the initial treatment of decompensated HF. When patients present to the clinic or emergency department with symptomatic HF, diuretics should be administered without delay. Patients receiving chronic diuretic therapy may need higher doses than patients with new-onset HF. In situations of diuretic "resistance," the addition of metolazone or chlorothiazide may be helpful. Some patients with perceived diuretic resistance may respond to loop diuretic administered as a continuous infusion rather than as scheduled bolus dosing. The treating physician should frequently monitor for electrolyte disturbances (hypokalemia, hypomagnesemia), renal injury, and lowered blood pressure during treatment with intravenous diuretics.

Some patients with chronic recurrent fluid overload (or even acute congestion) may benefit from restriction of fluid intake, especially in the setting of diminished diuretic responsiveness. The degree of fluid restriction should vary depending on the severity of fluid overload, refractoriness of diuretics, nutritional status of the patient, and electrolyte abnormalities such as hyponatremia. However, there are no data that show a clinical benefit of fluid restriction in children. One must also practice caution in infants because limited fluid intake may also lead to calorie restriction and limited growth.

The metabolic demands of the body are usually increased during HF exacerbation and may lead to muscle wasting. As well, high concentrations of neurohormones such as tumor necrosis factor α can lead to cardiac cachexia. Malabsorption of nutrients in the gut due to bowel wall edema and decreased perfusion also plays a role. The most important therapy for malnutrition in HF is the administration of appropriate HF medications, such as ACE inhibitors and β-blockers. Dietary supplementation may be necessary for some patients, and a formal assessment by an experienced dietitian may be helpful. There are few data for appetite stimulants in adults with HF, and the cardiovascular societies have made no recommendation regarding their use.

Inotropes

The ACC Foundation and the AHA have recommended against the routine use of inotropes in the treatment of decompensated HF in adults. However, inotropes still play an important role in the management of patients with symptomatic HF and evidence of poor perfusion or low blood pressure. In these patients, inotropic agents may be necessary to maintain circulatory function, relieve symptoms, and improve end-organ function.

Milrinone is a phosphodiesterase inhibitor that enhances inotropy and reduces afterload by increasing cyclic adenosine monophosphate. Milrinone also reduces pulmonary vascular tone and is less likely to cause tachycardia than other inotropic agents. Only a few studies have evaluated milrinone for the treatment of decompensated HF in adults and have shown only little, if any, clinical benefit. (36) In fact, milrinone may pose a greater risk of arrhythmias and death in adults with advanced HF. In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure study, adults with chronic HF were randomized to receive either an intravenous infusion of milrinone or placebo. There was no difference in length of stay between the patients taking milrinone and the placebo group, but arrhythmias and hypotension occurred at a greater frequency in patients randomized to receive milrinone.

Dobutamine

Dobutamine is an adrenergic agent frequently used to treat low cardiac output in adults with decompensated HF. The agent activates β-receptors in the heart and peripheral vasculature, increasing contractility of the myocardium and decreasing vascular tone. Although this physiologic effect might seem favorable, dobutamine infusions in patients with HF may cause more harm than good. (37) (38) The Flolan International Randomized Survival Trial showed that patients with symptomatic HF treated with dobutamine had a higher mortality rate than patients with HF who did not receive dobutamine. (38) Adverse effects of dobutamine include tachycardia, increased myocardial oxygen consumption, and increased incidence of atrial and ventricular arrhythmias. No controlled dobutamine studies have been performed in children with HF.

Dopamine

Dopamine is an adrenergic therapy that stimulates α- and β-receptors and can be considered in situations of cardiogenic shock or low cardiac output. It also stimulates dopaminergic receptors on the renal vasculature. At doses of 3 μg/kg per minute and higher, stimulation of β-1 receptors in the heart may enhance ventricular contractility and increase heart rate. At doses of 5 μg/kg per minute and higher, the α-receptor activity increases peripheral vascular tone and negates any peripheral vasodilation caused by β-2 receptor stimulation. (39) Epinephrine may also be considered in this situation. Although it can stabilize blood pressure and heart rate, epinephrine may also result in ischemia, atrial and ventricular arrhythmias, and increased myocardial oxygen consumption.

Despite the most optimized medical therapy, some children develop worsening and advanced end-stage HF with low cardiac output syndrome; MCS may be the only treatment option remaining for patients being considered for cardiac transplant. It can be used as a bridge to cardiac transplant or as a bridge to recovery in patients with potentially reversable disease processes, such as myocarditis or acute graft rejection. Outcomes with MCS are most successful when application is early, that is, before the patient develops significant end-organ injury. Careful consideration must be given to cases on an individual basis before committing to long-term support because clinical experience with chronic MCS is still limited.

Summary

- Substantial research has demonstrated that heart failure (HF) can be caused by a variety of disease processes that lead to a final common clinical syndrome consisting of ventricular dysfunction, elevated filling pressures, neurohormonal activation, and clinical symptoms. (2)
- Based on clinical research, common clinical features of HF in children include abdominal pain, decreased appetite, labored breathing, wheezing, diaphoresis, poor weight gain, hepatomegaly, and gallop rhythm. (6)
- Clinical studies have shown that diagnostic testing in HF may reveal cardiomegaly on chest radiography, abnormal cardiac rhythm on electrocardiography, decreased ventricular function and ventricular chamber enlargement on echocardiography, and elevated B-type natriuretic peptide concentration. (5)(7)(10)(11)
- Strong evidence supports the use of an angiotensin-converting enzyme (ACE) inhibitor with or without a β-blocker for the initial treatment of asymptomatic ventricular systolic dysfunction. (13)(14)(15)(16)(17)(18)(19)(20)(21)
- Consensus opinion and limited evidence support the use of a loop diuretic in patients with symptomatic HF. (5)(34)
- Clinical evidence suggests that patients with advanced HF should be considered for an aldosterone antagonist co-administered with an ACE inhibitor and a β-blocker. (35)
- If disease progresses to refractory symptoms, inotropic support may improve cardiac output and end-organ perfusion. Mechanical circulatory support may be indicated if a patient is considered a good candidate for cardiac transplant.

References for this article are at http://pedsinreview.aappublications.org/content/40/2/60.

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1. A 2-year-old boy with recurrent respiratory issues and gastrointestinal concerns is brought to the clinic for evaluation. The parents report that he is napping more frequently than a few months ago. He is less interested in his food and seems tired during the day. On cardiac examination, S1 is normal. S2 is single. There are third and fourth gallop heart sounds in diastole. The patient is referred to cardiology. Which of the following is the best initial test for the cardiologist to perform in the evaluation of this patient?
   A. Echocardiogram.
   B. Feeding evaluation.
   C. Holter monitor for 1 week.
   D. Sleep study.
   E. Trial of β-blocker medication.
2. A 3-year-old girl is brought to the clinic for evaluation of progressive fatigue and recurrent respiratory concerns. She was previously seen in the emergency department and was treated for wheezing with good response. She is otherwise healthy. Her physical examination today is significant for hepatomegaly. An echocardiogram shows bi-atrial enlargement. Which of the following is the most likely diagnosis in this patient?
   A. Aortic stenosis.
   B. Hepatitis.
   C. Idiopathic atrial flutter.
   D. Restrictive cardiomyopathy.
   E. Sequelae of Kawasaki disease.
3. A 10-year-old boy is being followed in the cardiology clinic for history of heart failure associated with mitral valve regurgitation. He remains asymptomatic and has demonstrated appropriate growth and development for his age. The cardiologist following him shares that the boy has impaired systolic function. Which of the following is the most appropriate next step in the management in this patient?
   A. Addition of an angiotensin-converting enzyme (ACE) inhibitor.
   B. Emergency mitral valve surgery.
   C. Nutrition evaluation and review of sodium intake.
   D. Trial of digoxin.
   E. Trial of oral milrinone.
4. A 9-year-old girl with a history of cardiomyopathy is followed in the cardiology clinic. She has hepatomegaly on examination and fatigue with exercise. She is taking enalapril for treatment of congestive heart failure. Which of the following is the most appropriate medication to be added to her treatment regimen??
   A. Alprazolam.
   B. Carvedilol.
   C. Dobutamine.
   D. Milrinone.
   E. Trazodone.

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5. A 10-year-old boy with a history of complex congenital heart disease and congestive heart failure is brought to the cardiology clinic for follow-up. He is taking enalapril and propranolol. He is fatigued during the day, and his parents are concerned that he is not able to participate in school activities owing to his fatigue. Which of the following is the most appropriate medication to be added to the treatment regimen of this patient?
   - A. Dobutamine.
   - B. Dopamine.
   - C. High-dose enalapril.
   - D. Milrinone.
   - E. Spironolactone.

Congestive Heart Failure in Children

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Novel Drugs of Abuse

George Sam Wang, MD,*† Christopher Hoyte, MD†‡

*Section of Emergency Medicine and Medical Toxicology, Department of Pediatrics, University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, Aurora, CO

†Rocky Mountain Poison and Drug Center, Denver Health Hospital, Denver, CO

‡Department of Emergency Medicine and Medical Toxicology, University of Colorado Anschutz Medical Campus, University Hospital, Aurora, CO

Education Gaps

1. Although adolescent use of novel drugs of abuse is less common than traditional illicit drug use, it can be associated with significant morbidity and mortality.
2. Pediatricians and emergency medicine physicians should be knowledgeable about novel drugs of abuse to properly prevent and identify their abuse.

Objectives

After completing this article, readers should be able to:

1. Describe what is known about the epidemiology of novel drugs of abuse in adolescents.
2. Highlight the unique challenges associated with novel drugs of abuse.
3. Describe the pathophysiology, symptoms, and treatment for novel drugs of abuse.

Abstract

Novel drugs of abuse are synthetic illicit drugs, or analogues of known illicit drugs, that can be more potent. Novel drugs of abuse are often labeled as *designer drugs, research chemicals, legal highs,* or *psychoactive substances*. They are often sold as designated legal or nondrug products, such as incense, plant food, or bath salts, with labeling such as "Not for Human Consumption" or "For Use in Research Only." The prevalence of use of novel drugs of abuse is difficult to determine because specific drugs, compounds, and availability of these drugs are constantly evolving. Changes in chemical structures lead to heterogeneity in physiologic response and clinical symptoms, even within the same category of drug. Pediatricians and emergency medicine physicians should be knowledgeable about novel drugs of abuse and their resulting symptoms for prevention and identification of their use.

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ABBREVIATIONS

CNS	central nervous system
DEA US	Drug Enforcement Administration
GABA	γ-aminobutyric acid
GHB	γ-hydroxybutyrate
LSD	lysergic acid diethylamide
MTF	Monitoring the Future
PCP	phencyclidine
SC	synthetic cannabinoid

NOVEL DRUGS OF ABUSE

In the most recent National Survey on Drug Use and Health, approximately 2.2 million, or 8.8%, of adolescents aged 12 to 17 years admitted to using any illicit drug, including marijuana, prescription medications, cocaine, hallucinogens, methamphetamines, inhalants, and heroin. (1) In 2017, the Monitoring the Future (MTF) survey reported that 9.4% of eighth-, 10th-, and 12th-graders admitted to using any illicit drug other than marijuana in the past year. (2) Novel drugs of abuse are newer synthetic illicit drugs, or analogues of known illicit drugs, that can be more potent and difficult to identify and detect. Prevalence of use is challenging because the specific drugs, compounds, and availability of these drugs are constantly changing. Despite the lack of accurate epidemiologic data, novel and synthetic drugs of abuse are a public health concern affecting adolescents. The use of novel drugs is associated with significant morbidity and mortality and can lead to significant medical consequences and outcomes from acute intoxication and associated polysubstance use. (3)(4)

Novel drugs of abuse are often labeled as *designer drugs, research chemicals, legal highs,* or *psychoactive substances*. Although the US Drug Enforcement Administration (DEA) has made distribution and use of many of these drugs illegal, there are several challenges that make monitoring and detection of these drugs difficult. (5) Drug manufacturers and distributors may sell them as designated legal or nondrug products, such as incense, plant food, or bath salts. They will also be sold with labeling such as “Not for Human Consumption” or “For Use in Research Only” to avoid any responsibility for their abuse and misuse. Drug manufacturers may develop the chemical to resemble other illicit drugs and slightly change the chemical structure, which makes them difficult to detect. Standard urine drug immunoassays do not detect these drugs, although detection may be performed in reference laboratories, if available. Changes in chemical structures lead to a heterogeneity in physiologic response and clinical symptoms from the same category of drug (Table). For example, synthetic cannabinoid (SC) intoxication can lead to mild symptoms such as sedation or more severe consequences such as seizures, hyperthermia, psychomotor agitation, and death. (6)

Many novel drugs of abuse are sold in convenience stores, publicly exchanged, and some are easily found on the Internet for purchase. The Dark Web, a part of the World Wide Web that is accessible only using specific coding or software, is also a potential source of distribution. (7) Contamination and quality control has been a long-standing problem with illicit drugs, and novel drugs of abuse are no exception. Examples of contaminants in traditional illicit drugs of abuse are the addition of fentanyl in heroin or levamisole in cocaine. (8)(9)(10)(11)(12)(13)(14) Because there is no regulatory or oversight process in the drug manufacturing, the content or potency will also vary. Local public health emergencies and outbreaks have occurred from the distribution and use of novel drugs that are found to be significantly toxic or potent. (15)(16)(17)(18)(19)(20)

Because these drugs are difficult to detect, diagnosis is most often made by history, either by a witness or the patient, or by symptoms consistent with reported use of the drug. Most published research on novel drugs of abuse are case reports, media accounts of local outbreaks, and novel analytical techniques to help with detection. Drug manufacturers and recreational users will describe drug dosing and symptoms using Internet sources such as Erowid, Psychonautwiki, and Bluelight. (21)(22)(23)

SYNTHETIC CANNABINOIDS

In 2010, more than 11,000 emergency department visits were associated with SCs, and 75% were in adolescents and young adults aged 12 to 29 years. (24) Fortunately, use among adolescents seems to have decreased. According to the MTF survey, past-year use of SCs in adolescents has declined since 2012, from 11.4% to 3.5%. (2)(25)(26) Despite this decrease, adolescents represent a large proportion of recreational users. In a multicenter prospective observational study of consultations performed by medical toxicologists, adolescents aged 13 to 18 years accounted for approximately 25% of patients presenting to health-care facilities for acute SC intoxication. (27) Comorbidities associated with SC use in adolescents include depressive symptoms and marijuana, alcohol, and polysubstance use. (3)(4)

Synthetic cannabinoids are chemically synthesized analogues of natural cannabinoids; they are not cannabis products. They are sold as the chemical itself in powered form, or sprayed or applied to marijuana, dried herbs/plants, or other hallucinogenic plants. They are sometimes commonly referred to as *K2, Spice,* or *Buddha*. More than 200 known SCs have been identified. (28) Synthetic cannabinoids are agonists at the cannabinoid receptors in the central nervous system (CNS) that result in their psychoactive effects. They can have similar or increased potency on cannabinoid receptors compared with natural cannabinoids. Clinical symptoms are variable; common mild symptoms include ataxia, sedation, mydriasis, and tachycardia. More severe symptoms reported include psychomotor agitation, psychosis, seizures, hallucinations, delirium, rhabdomyolysis, respiratory depression, and acute kidney injury. (29)(30)(31)(32)(33) Ischemic stroke, subarachnoid hemorrhage, myocardial ischemia and infarction, and death have also been reported. (34)(35)(36)(37) Treatment consists of sedation (including benzodiazepines, antipsychotics) to control psychomotor agitation and supportive care for associated end-organ toxicity. Standard urine drug immunoassays will not detect SCs and will not result in a positive tetrahydrocannabinol or respective metabolites. Confirmatory reference laboratory assays are available for some SCs, but they do not return in a timely manner to affect clinical care. However, as more SCs are developed, many are not detectable with available confirmatory assays.

SEDATIVES

Phenibut

Phenibut (β-phenyl-γ-aminobutyric acid hydrochloride) was discovered and introduced in clinical practice in Russia in the 1960s for the treatment of anxiety, alcohol withdrawal, and insomnia. (38)(39) It is widely available for purchase on the Internet for recreational use. (40) Phenibut and its analogues have similar psychopharmacological action as baclofen and act primarily on γ-aminobutyric acid (GABA)-B receptors. It also stimulates GABA-A and dopamine receptors and antagonizes β-phenethylamine. The most reported route of phenibut use is by ingestion rather than by nasal insufflation or injection. (39)

Onset of symptoms is reported to occur 2 to 4 hours after oral ingestion and may last up to 24 hours. Symptoms from phenibut use include sedation, CNS depression, and ataxia. (38)(39)(40)(41)(42) Symptoms can be exacerbated when coingested with other sedatives/hypnotics. Other, more severe symptoms include hallucinations, agitation, and seizures. Treatment should be focused on ensuring adequate ventilation and providing sedation for psychomotor agitation. Similar to other GABA-A and GABA-B agonists, one should expect withdrawal to occur with abrupt cessation after chronic use with similar associated symptoms, including delirium, tremor, and seizures. (43)

γ-Hydroxybutyrate and Associated Compounds

According to the MTF, 0.7% of 12th-graders admit to past-year use of γ-hydroxybutyrate (GHB), (2) a federal schedule I drug. (44) Sodium oxybate, which is a GHB-containing pharmaceutical product, is a schedule III drug for cataplexy and narcolepsy. The endogenous GABA neurotransmitter is metabolized in small amounts to GHB naturally. 1,4-Butanediol and γ-butyrolactone are both metabolized to GHB and can have similar clinical sequelae. These chemicals can be found in printing ink, cleaning agents, automotive products, and adhesives.

Most exogenous GHB is ingested, insufflated, or injected in powder or liquid form. They are GABA-B receptor agonists, which clinically lead to sedation, CNS depression, nausea, bradycardia, and respiratory depression. Classically, GHB will lead to rapid onset of symptoms, with peak concentrations within 30 to 40 minutes, followed by a rapid recovery a few hours later. (45) Respiratory support is the mainstay of treatment. Withdrawal symptoms have been described after chronic abuse. (46)(47) Reference laboratory analysis can be performed to detect GHB, 1,4-butanediol, or γ-butyrolactone.

Kava

Kava is derived from the *Piper methysticum* plant. It can be referred to as *awa, kew,* or *tonga*. It can be smoked or prepared as a beverage or tea and is often used for relaxation or to treat anxiety. The active ingredients are kava lactones, which include methysticin, dihydromethysticin, kawain, and yangonin. (48) Although the exact mechanisms of action are unknown, kava lactones are thought to modulate the GABA neurotransmitter pathway, leading to the mild sedating clinical effects.

Acute use of kava is not expected to cause neuropsychiatric symptoms severe enough to require acute intervention or health-care evaluation. Several kava lactones have been shown to have CYP450 interactions (potent inhibitors), which could lead to drug interactions. (49) Long-term use has been associated with dermatitis, hepatotoxicity, nausea, and indigestion. (50)(51)

HALLUCINOGENS/PSYCHOACTIVE DRUGS

Phencyclidine and Analogues

Phencyclidine (PCP), ketamine, and their novel analogues are arylcyclohexamines that exhibit their dissociative effects by antagonizing *N*-methyl-D-aspartate receptors. (52) The Substance Abuse and Mental Health Services Administration reported that 2.5% of adolescents and young adults 12 years and older have used PCP in their lifetime. (1) Many novel PCP analogues have become available, including methoxetamine, 3- and 4-methoxyphencyclidine. (53)(54)(55)(56)(57) In contrast to PCP, ketamine is not well absorbed by the oral route, with limited bioavailability and significant first-pass metabolism. Also, PCP has a longer half-life and duration of action than ketamine. Ketamine has 10% of the affinity for the *N*-methyl-D-aspartate receptor than PCP, whereas some other analogues, such as 3- methoxyphencyclidine, have higher affinity than PCP. (57)

Common symptoms include tachycardia, nystagmus, hypertension, euphoria, nausea, and vomiting. More serious effects include psychosis, delirium, hallucinations, and agitation. Users describe being in the "K-hole" when having their dissociated experiences. Life-threatening complications reported include coma, hypoventilation, apnea, and seizures. Treatment for PCP intoxication includes limiting external stimulation and giving sedation for psychomotor agitation, including benzodiazepines. Antipsychotics can be considered, but caution should be used because this may exacerbate hyperthermia, lower the seizure threshold, and have associated adverse effects, such as dystonic reactions. Phencyclidine is detected on some standard urinary drug immunoassays; false-positives can occur with exposures to dextromethorphan and diphenhydramine. Phencyclidine and ketamine analogues may not reliably cross-react with the PCP urine immunoassay.

Lysergic Acid Diethylamide and Associated Analogues and Other Serotonergic Agonists

Lysergic acid diethylamide (LSD) has been abused for decades for its hallucinogenic properties. The MTF reports that less than 3% of all eighth-, 10th-, and 12th-graders admitted to using LSD in the previous 12 months. (2) There are several LSD analogues available, including N-allyl-nor-lysergic acid N,N diethylamide, and lysergic acid 2,4-dimethylazetidide. (58) Lysergic acid diethylamide and associated analogues are typically used in powder or blotter form via oral or sublingual administration and mediate their symptoms by activation of the serotonin 5HT-2A receptor. (59)(60) Analogues of LSD have similar onsets of action, but many of them have less reported euphoria and strength of effect compared with LSD. (59) 2-C drugs are hallucinogenic phenethylamines, which include 4-iodo-2,5-dimethoxyphenethylamine and 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl) phenethylamine. (61)(62)(63)(64)(65)(66)(67)(68) They have several slang terms, including *25i, 2-C, 2-I, 2-CB, NBOMB,* and *N-BOMB*. They were initially developed for research purposes to study the 5HT-2A receptor because they are potent serotonin agonists. More analogues continue to be developed by substitutions to the base phenethylamine structure. Similar to LSD, 2-C drugs are often sold on blotter paper and used sublingually or orally.

Symptoms from both LSD analogues and 2-C compounds are variable but mostly consist of hallucinations, euphoria, tachycardia, and hypertension. Suicidality was described in a case report. (64) More significant adverse effects include psychosis, agitation, seizures, hyperthermia, rhabdomyolysis, kidney injury, serotonin toxicity, and death. (65)(66)(67)(68) Laboratory abnormalities that may be found include elevated creatinine kinase, leukocytosis, hyperglycemia, and acidosis. Treatment is similar to that for other etiologies of agitated delirium and psychosis, including sedation with agents such as benzodiazepines and antipsychotics. (65) There has been a report of using cyproheptadine for serotonin toxicity resulting from a 2-C compound. (64) Routine testing for LSD analogues and 2-C compounds are not routinely available, and most exposures are determined by history and physical examination. Similar to other novel drugs of abuse, analytic detection methods may be limited due to the constant evolution of these compounds.

OPIOID/OPIATE ANALOGUES

Fentanyl, Analogues, and Synthetic Opioids

The MTF reported that trends in lifetime prevalence of narcotic use other than heroin in 12th-graders have declined from 13.4% in 2006 to 6.8% in 2017. (2) Fentanyl is a short-acting synthetic opioid agonist approximately 100 times more potent than morphine. The DEA has found a significant increase in fentanyl seized by law enforcement nationwide by almost 400% from 2013 to 2014. (69) The increase in use of fentanyl as a heroin substitute (intentionally or through adulteration) has been primarily responsible for an increase in US drug overdose deaths. Fentanyl is used via inhalation, intravenous access, or parenteral administration. Transdermal fentanyl in the form of a patch contains enough drug to create a transdermal gradient sufficient to achieve steady-state plasma concentrations for 3 days. After a fentanyl patch is considered exhausted, approximately 50% of the total dose remains. Fentanyl patch abuse can occur by application of 1 or more patches to the skin, by application of heat and an occlusive dressing, or by extraction of the drug from the patch reservoir. (70)

Many fentanyl analogues also exist that have been implicated in overdose deaths: carfentanyl (10,000 times more potent than morphine), sufentanil, and alfentanil. (71)(72) U-47700, sometimes referred to as *pink,* is another popular illegal synthetic opioid in which abuse has led to high mortality and morbidity. (71)(73)(74) Synthetic opioids have also been sold and mislabeled as diverted prescription opioid analgesics.

After overdose, patients present with the typical opioid toxidrome: CNS depression, miosis, and respiratory depression. Similar to the treatment of other opioid intoxication, the focus should be respiratory support by either mechanical ventilation or use of naloxone. Although fentanyl is more

TABLE. **Novel Drugs of Abuse and Associated Clinical Symptoms**

DRUG CATEGORY	CLINICAL SYMPTOMS CARDIOVASCULAR	NERVOUS SYSTEM	OTHER
Synthetic cannabinoids	Tachycardia, hypertension, myocardial ischemia	Agitation, sedation, psychosis, seizures, delirium, ataxia	Hyperthermia, metabolic acidosis, acute kidney injury, rhabdomyolysis
Phenibut	Bradycardia, hypotension	Sedation, coma, ataxia, nystagmus	Respiratory depression
γ-Hydroxybutyrate	Bradycardia, hypotension	Rapid-onset sedation and coma, ataxia, nystagmus	Respiratory depression
Phencyclidine and analogues	Tachycardia, hypertension, flushed	Agitation, delirium, sedation, mydriasis or miosis, ataxia, nystagmus, hyperreflexia, hallucinations	Hyperthermia, metabolic acidosis, acute kidney injury, rhabdomyolysis
Lysergic acid diethylamide and serotonergic agonists	Tachycardia, hypertension	Auditory and visual hallucinations, nystagmus, ataxia, psychosis, delirium, mydriasis, coma, hyperreflexia, clonus	Hyperthermia, metabolic acidosis, acute kidney injury, rhabdomyolysis
Fentanyl and synthetic opioids	Bradycardia, hypotension	Euphoria, sedation, coma	Respiratory depression
Cathinones	Tachycardia, hypertension	Agitation, psychosis, delirium, mydriasis, seizures	Hyperthermia, metabolic acidosis, acute kidney injury, rhabdomyolysis

potent than heroin, the dose of naloxone required to reverse respiratory depression seems to be similar to that of other common opioids. (75) The binding affinity of fentanyl at the μ opioid receptor is similar to that of morphine and naloxone. (76)(77) However, if an exposure involves large quantities of fentanyl, or certain analogues, such as sufentanil, higher doses of naloxone may be required for reversal. (76) Fentanyl, fentanyl analogues, and other illicit synthetic opioids will not be detected on a standard urine drug immunoassay for opiates. Diagnosis should be made on history and clinical suspicion. Reference laboratories have detection methods for some of these novel opioid analogues.

Loperamide

Loperamide is an insoluble meperidine analogue that is used to treat diarrhea. Although loperamide has been used for decades as an antidiarrheal, its use as a drug of abuse is novel. This medication is available without a prescription, and the paucity of adverse patient outcomes reported in the medical literature suggests that the safety profile of this agent is good. There is limited oral bioavailability of loperamide, thus large overdoses are required to achieve euphoria. There are several reports of use and abuse of loperamide for self-treatment of opioid addiction and to achieve euphoria similar to opioids. (78)(79)(80)(81)(82) Clinical signs of respiratory depression, miosis, and CNS depression may be present in large overdoses. The more concerning adverse effect is cardiac dysrhythmia. Loperamide abuse may result in significant QT-interval prolongation and potentially life-threatening cardiac dysrhythmias. (83)(84)(85) Treatment consists of respiratory support and naloxone administration, if necessary. (86) Cardiac dysrhythmias should be treated accordingly for the specific cardiac abnormality. Detection of loperamide and its metabolites can be obtained from reference laboratories.

Kratom

Kratom, or *Mitragyna speciosa*, is derived from a tree native to Asia and Africa and has been used to enhance productivity in manual laborers and to treat chronic pain and opioid withdrawal. (87) In the United States, kratom is primarily abused for euphoria and stimulant properties, as well as for pain, mood swings, and opioid-related withdrawal. (88)(89) There has been a 10-fold increase in regional poison center calls involving kratom: from 26 in 2010 to 263 in 2015. (90) Kratom produces both stimulant effects and opioid analgesic effects. The kratom alkaloids mitragynine and 7-hydroxymitragynine activate μ-, δ-, and κ-opioid receptors. Commonly reported symptoms include altered mental status, agitation, CNS depression, and tachycardia. (91) Hepatotoxicity and cholestasis have also been reported from kratom use. (92)(93)(94) There have been case reports of deaths associated with kratom use, but co-ingestants were also detected on postmortem examination. (95)(96)

Detection of mitragynine and its metabolites can be performed by reference laboratories.

STIMULANTS

Catha edulis, commonly known as khat, is a plant that is commonly used as a stimulant in Africa and Middle Eastern countries such as Yemen. Leaves of the plant are often chewed, and the active ingredient, cathinone, is absorbed. As the leaves of the plant age, cathinone is degraded to cathine, which has about one-tenth the stimulant effect of D-amphetamine. (97)(98) The primary effects of khat are agitation, increased alertness, insomnia, euphoria, anxiety, and hyperactivity. Khat chewing is associated with cardiac and gastrointestinal complications. (97)(98)

Synthetic cathinones are popular novel drugs of abuse and are easily purchased through the Internet. The abuse of synthetic cathinones is widely reported via the media, which sometimes refers to these drugs as *zombie drugs*. (99)(100) Similar to SCs, synthetic cathinones are often sold as nondrug products such as bath salts or plant food. They are labeled as “Not for Human Consumption” to circumvent controlled substances legislation. Synthetic cathinones include methylone, mephedrone, butylone, methylenedioxypyrovalerone, dimethylcathinone, ethcathinone, ethylone, and 3-and 4-fluoromethcathinone. (99)(100) They have properties similar to amphetamines and have sympathomimetic effects, in addition to significant psychosis. (101) Similar to methoxydeoxymethamphetamine (ecstasy), some synthetic cathinones have been reported to cause hyponatremia, although the mechanism is unclear. (102)(103)(104)(105) Other reported complications include acute kidney injury and sudden cardiac death. (106)(107)(108)(109)(110) On September 7, 2011, the DEA used its emergency scheduling authority to make possession or sale of methylenedioxypyrovalerone, methylone, and mephedrone illegal. (111) Symptomatic and supportive care is the mainstay for the treatment of cathinone toxicity. This includes sedation with benzodiazepines and antipsychotics and control of psychomotor agitation to prevent significant acidosis and end-organ toxicity. Cathinones are not identified on standard urine drug immunoassays, and reference laboratory testing is needed if detection is indicated.

Summary

- Novel drugs of abuse are also called *designer drugs, research chemicals, legal highs,* or *psychoactive substances.* They are often sold with labels warning “Not For Human Consumption.”
- Development of drug analogues by changing chemical structures leads to a heterogeneity in physiologic response and symptoms within the same category of drug. (5) This also makes laboratory detection difficult and limited.
- Based on observational studies, expert opinion, and case reports, diagnosis should be based on history and physical examination findings, and treatment should focus on symptomatic and supportive care.

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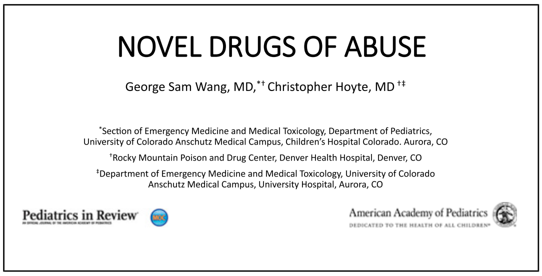

NOVEL DRUGS OF ABUSE

George Sam Wang, MD,*† Christopher Hoyte, MD †‡

*Section of Emergency Medicine and Medical Toxicology, Department of Pediatrics, University of Colorado Anschutz Medical Campus, Children’s Hospital Colorado. Aurora, CO

†Rocky Mountain Poison and Drug Center, Denver Health Hospital, Denver, CO

‡Department of Emergency Medicine and Medical Toxicology, University of Colorado Anschutz Medical Campus, University Hospital, Aurora, CO

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1. A 16-year-old high school student is brought by emergency medical services to the emergency department on a Saturday at 9 pm with acute onset of ataxia, sedation, mydriasis, tachycardia, hallucinations, and agitation. The patient is accompanied by her 16-year-old friend who tells you that they were at a party where many "designer drugs" were being exchanged. You suspect marijuana or a similar drug. A urine toxicology screen is performed and is negative. Which of the following best explains the reason why the detection of designer drugs is so difficult?
   A. Designer drugs are metabolized very quickly and are largely out of the system in minutes.
   B. Polysubstance abuse causes interference in the assays.
   C. Slight alterations in the chemical formula compared with the parent compound cause them to be undetectable in standard urine drug immunoassays.
   D. The amount of drug in the system is too small for standard detection methods.
   E. The ingestion of alcohol masks designer drugs.
2. On further questioning of the friend who accompanied the patient in question 1 to the emergency department, she states that the patient may have ingested "Spice" or "Buddha." In which of the following general categories of designer drugs does Spice belong?
   A. Amphetamines.
   B. Benzodiazepines.
   C. Hallucinogenic drugs.
   D. Opioid analogues.
   E. Synthetic cannabinoids.
3. A 16-year-old boy presents to the emergency department with tachycardia, hypertension, nystagmus, psychosis, and agitation. You suspect phencyclidine overdose. Which of the following is the best initial treatment for this patient?
   A. Antipsychotics.
   B. Benzodiazepines.
   C. β-Blockers.
   D. Insulin and glucose.
   E. Naloxone.
4. A 15-year-old boy is brought by emergency medical services to the emergency department with central nervous system depression, miosis, and respiratory depression. There are no friends or family members present to provide further information about the substance ingested. You turn to your medical student and mention that this is a classic toxidrome for a certain class of drugs. Overdose with which of the following substances is most likely to present with the classic toxidrome seen in this patient?
   A. Amphetamines.
   B. Benzodiazepines.
   C. Cannabinoids.
   D. Hallucinogens.
   E. Narcotics.

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5. The parents of a 14-year-old who was brought to the emergency department with likely synthetic cathinone ingestion want to know how he could have gotten the drug since he is homeschooled and lives a solitary life on a family farm. Which of the following features of cathinone best explains this patient's easy access to these dangerous drugs?

   A. Commonly prescribed for patients with attention-deficit/hyperactivity disorder.
   B. Derivatives of soybeans commonly found on family farms.
   C. Easy to extract from simple bread mold.
   D. Found in many common over-the-counter cold and flu preparations.
   E. Sold legally as bath salts over the Internet.

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Index of Suspicion

1 A Medically Complex 10-month-old Boy with Lethargy

Michael S. Toce, MD, MS,[*,†] Todd W. Lyons, MD, MPH[*]

[*] *Division of Emergency Medicine, Department of Medicine, Boston Children's Hospital, Boston, MA*

[†] *Harvard Medical Toxicology Program, Boston, Children's Hospital, Boston, MA*

EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Toce and Lyons have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 10-month-old boy status-post hematopoietic stem cell transplant for leukemia, with type IV renal tubular acidosis secondary to cyclosporine and resolved hypertension, presents to the emergency department with lethargy. He had been difficult to awaken since this morning. His family denies fever, other symptoms suggestive of infection, or trauma. Current medications include cyclosporine, sulfamethoxazole/trimethoprim, and citric acid. His family denies any possibility of unintentional toxic ingestion.

On examination he is lethargic, with a Glasgow Coma Scale score of 10 (eye opening = 2, verbal = 3, motor = 5). His temperature is 98.6°F (37°C), heart rate is 102 beats/min, respiratory rate is 22 breaths/min, and blood pressure is 84/35 mm Hg. The head is without signs of trauma. Pupillary examination is notable for miosis (2mm-1mm) bilaterally. A nasogastric tube is affixed to the right cheek. There is no meningismus. The chest, cardiac, and abdominal examination results are all within normal limits. The neurologic examination is notable for lethargy but without other focal deficits.

A complete blood cell count with a differential count reveals a white blood cell count of 5.6/μL (0.01$\times 10^9$/L) (71% neutrophils), a hemoglobin level of 8.0 g/dL (80 g/L), and a platelet count of 129$\times 10^3/\mu$L (129$\times 10^9$/L). Serum chemistry values (including calcium, magnesium, and phosphorous) are normal aside from a bicarbonate level of 19 mEq/L (19 mmol/L). A urine toxicology screen is negative for opiates, cannabinoids, benzodiazepines, barbiturates, and cocaine. Findings from a noncontrast head computed tomographic scan are within normal limits. Results of cerebrospinal fluid studies are all within normal limits. The patient is admitted to the hospital for further monitoring, and the diagnosis is made by an astute nurse.

DISCUSSION

The differential diagnosis of altered mental status in children is broad and includes infectious, neurologic, metabolic, traumatic, and toxicologic causes. The combination of altered mental status and miosis raised concern for a toxicologic etiology, but no exposure could be identified. However, on hospital admission a nurse performing her assessment noted the unusual appearance of the dressing used to affix the nasogastric tube. The dressing was removed and found to be two 0.1-mg/day clonidine patches, which had been previously prescribed to treat hypertension. The family had mistaken the clonidine patches for a simple adhesive patch and placed them in the same bag they used to store nasogastric tube dressings. After their removal, the child was monitored and returned to his neurologic baseline within 24 hours. The exposure to clonidine was missed by the medication history that focused exclusively on medications taken orally.

Medication errors are common in pediatric inpatient settings. A prospective cohort study of pediatric inpatients found an error rate of 5.7 errors for every 100 medication orders. The most common error type was incorrect dose (28%), followed by incorrect route (18%). (1) The medical reconciliation is a type of medication history that is used to ensure that all of the patient's medications are accounted for and properly ordered when a patient is admitted to the hospital. Electronic medical reconciliation decreases admission medical reconciliation errors, with 1 study reporting a 53% reduction in nonintercepted errors. (2) An accurate medication history, including oral, topical, intranasal, and nonprescription medications, in addition to herbal supplements and vitamins, is necessary to reduce medication errors.

Clonidine exposure in this child could have been suspected based on the constellation of central nervous system (CNS) depression and miosis. Clonidine is used in children for the treatment of attention-deficit/hyperactivity disorder, Tourette syndrome, other behavioral conditions, sedation and withdrawal in the ICU, and hypertension. (3)(4)(5) Clonidine belongs to the imidazoline class of medications, which also includes guanfacine, dexmedetomidine, and tizanidine. It is available in liquid, pill, and transdermal (patch) preparations. Clonidine patches come in 2-, 5-, and 7.5-mg strengths, which release 0.1, 0.2, and 0.3 mg/day of clonidine, respectively. Patches are replaced every 5 to 7 days. Residual drug can remain in the patch even after removal, and cases of toxicity due to ingestion of a patch have been reported. (6)

The mechanisms by which clonidine induces sedation and lowers blood pressure and heart rate are incompletely understood. (7) Clonidine binds to presynaptic α_2-adrenergic receptors in the locus coeruleus in the pons, producing sedation, and in the nucleus tractus solitarii in the medulla, leading to a decrease in norepinephrine release, which contributes to the decrease in heart rate and blood pressure. In addition to being an α_2-adrenergic receptor agonist, clonidine binds to the imidazoline-1 receptor in the rostral ventrolateral medulla in the CNS and in the periphery. This binding produces a decrease in heart rate, blood pressure, and myocardial contractility and is thought to be responsible for the cardiovascular adverse effects seen during clonidine administration and overdose. (8)

The use of clonidine in children is increasing. (9) As clonidine's clinical use has increased, so have unintentional pediatric exposures. (10) Between 2000 and 2011 there was a significant yearly increase in pediatric exposures to central α_2-adrenergic receptor agonists (clonidine, guanfacine, and tizanidine) of nearly 6% per year. (11) In 2015, there were 3,938 cases of clonidine exposure in children younger than 20 years. (12)

The diagnosis of clonidine overdose/toxicity is a clinical one based on a detailed exposure history and physical examination. Symptoms of clonidine overdose are directly related to sympathetic depression and include lethargy and altered mental status, respiratory depression, bradycardia and hypotension, and miosis. (11) Paradoxically, early in exposure, patients can develop hypertension due to peripheral α-adrenergic receptor stimulation. (10) The constellation of symptoms associated with clonidine toxicity is sometimes mistaken for opioid toxidrome given the significant overlap in symptoms (miosis, respiratory depression, CNS depression). Providers should have a high index of suspicion for clonidine exposure in patients who present with CNS depression, bradycardia, and hypotension and have access to clonidine. Serum clonidine concentrations can be obtained, but results typically take several days, limiting their clinical utility. Similarly, standard urine drug testing will not detect clonidine.

Treatment of clonidine overdose includes supportive care with specific attention to the airway, breathing, and circulation. Respiratory depression should be treated with positive pressure ventilation. End-tidal carbon dioxide monitoring provides one mechanism for monitoring respiratory effort. Significantly obtunded children who are not protecting their airway should be intubated, although this is rare. Symptomatic bradycardia can be treated with atropine. Patients who are hypotensive should receive isotonic fluids. However, the need for vasopressor agents is uncommon. Decontamination with charcoal can be considered for children who present early after ingestion, presuming they are able to safely swallow and protect their airway. A careful skin examination should be performed, and any patches should be removed. Naloxone has emerged as a potential treatment for clonidine toxicity in children. Case reports have demonstrated improvement in mental status and respiratory effort in children receiving naloxone after clonidine exposure. (13)(14) A recent retrospective cohort analysis of pediatric clonidine exposures showed that naloxone reversed somnolence in 40 of 51 patients. (15) Asymptomatic children should be observed in a monitored setting for 8 hours from the time of ingestion. Symptomatic patients should be admitted for overnight cardiopulmonary monitoring. Most children do well with good supportive care, and fatalities associated with clonidine use are extremely rare. (12)

Lessons for the Clinician

- As clonidine use in children and adults has increased, so have unintentional pediatric exposures.
- Clonidine formulations include patches, which may be missed by some medication histories.
- Clonidine overdose presents with central nervous system depression, respiratory depression, bradycardia, hypotension, and miosis.
- Treatment of clonidine overdose includes management of the airway, breathing, and circulation, including the use of atropine for bradycardia, as well as fluids for hypotension.
- Naloxone has been used with varying levels of success but should be considered in patients with severe, symptomatic clonidine overdose given its wide safety margin.

References for this article are at http://pedsinreview.aappublications.org/content/40/2/79.

Case 1: A Medically Complex 10-month-old Boy with Lethargy

Michael S. Toce and Todd W. Lyons

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Index of Suspicion

2

A 13-year-old Boy with a Perplexing Rash

Shafee Salloum, MD,* Aphton Lane, DO†

*Department of Pediatric Hospital Medicine, Dayton Children's Hospital, Dayton, OH
†Wright Patterson AFB/Department of Pediatrics, Wright State University/Boonshoft School of Medicine, Dayton, OH

AUTHOR DISCLOSURE Drs Salloum and Lane have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 13-year-old boy presents to the emergency department with a fever for 1 day and a worsening rash for 1 month. He initially took amoxicillin because the rash was thought to be due to scarlet fever. The amoxicillin was changed to azithromycin after 3 days due to concern for allergic reaction after the development of facial swelling. A week after completion of azithromycin therapy the patient was prescribed prednisone due to worsening of his rash, which became pruritic with drainage from some lesions. A review of systems is otherwise negative. The patient has no eczema, food, or drug allergies. He has no significant medical history other than a recent diagnosis of bipolar disorder for which he started taking carbamazepine 2 months before his presentation to the emergency department. He is up to date on his immunizations, without known sick contacts. Physical examination reveals an uncomfortable child in mild distress complaining of pruritus. His temperature is 102.2°F (39°C), heart rate is 134 beats/min, blood pressure is 117/69 mm Hg, respiratory rate is 20 breaths/min, and oxygen saturation is 99% on room air. He has a diffuse maculopapular erythematous rash over his torso and extremities (Fig). The rash is most concentrated on his face, neck, and upper trunk, with the flexural creases being the most involved. No oral lesions are noted, but he does have facial edema with cracked lips. Cervical and groin lymph nodes are enlarged. The rest of his examination findings are unremarkable. Laboratory evaluation reveals a white blood cell count of $23.7 \times 10^3/\mu L$ ($23.7 \times 10^9/L$), with 30% neutrophils, 9% bands, 11% lymphocytes, and 50% eosinophils. The absolute eosinophil count is $11.85 \times 10^3/\mu L$ ($11.85 \times 10^9/L$). A peripheral smear shows atypical lymphocytes. Liver tests are significant for elevated alanine aminotransferase and aspartate aminotransferase levels of 157 U/L (2.62 μkat/L) and 77 U/L (1.29 μkat/L), respectively. He has normal albumin, bilirubin, and electrolyte levels and renal function test results. A blood sample is sent for culture, and he is started on vancomycin for concern of resistant *Staphylococcus aureus* cellulitis. The constellation of history and laboratory results helps in making the final diagnosis.

DISCUSSION

Diffuse skin rash and peripheral eosinophilia raised a concern for an adverse drug reaction. Carbamazepine was a new medication for the patient, which

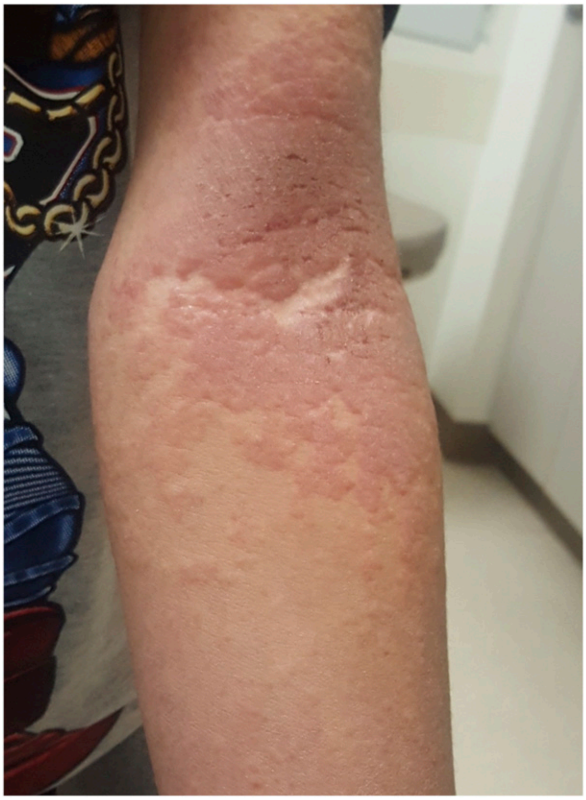

Figure. Skin eruption in the patient's upper extremity.

was started 1 month before the rash onset. Subsequently, the patient was diagnosed as having drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. DRESS is a rare, potentially life-threatening adverse reaction to many drugs, most commonly sulfonamides and aromatic anticonvulsants (eg, phenytoin and carbamazepine). Many other drugs have been implicated as well. The incidence of DRESS ranges from 1 in 1,000 to 1 in 10,000 drug exposures. DRESS can be more difficult to diagnose compared with other adverse drug reactions due to the presence of a longer latency period, which typically ranges from 3 to 8 weeks. There is a genetic component that predisposes HLA-A*3101–positive individuals to develop DRESS if exposed to carbamazepine. The clinical picture of DRESS is characterized by a severe skin eruption as well as potential systemic symptoms, including fever, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement. Skin rash is the most frequently reported symptom and usually involves more than 50% of the body, with or without facial edema. The most commonly encountered skin manifestation of DRESS syndrome is an erythematous morbilliform rash, in contrast to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which are bullous disorders of the skin with appearance similar to burn injuries. DRESS can also be distinguished from SJS/TEN by the absence of significant mucosal involvement, as well as the presence of marked eosinophilia (eosinophil count $>700/\mu L$ ($0.7 \times 10^9/L$)). The pathogenesis of DRESS is not completely understood. Reactivation of human herpesvirus (human herpesvirus 6 and 7 and Epstein-Barr viruses) has been discussed as potentially relevant in some patients.

Diagnosis and Treatment

The European Registry for Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system is used to aid the diagnosis of DRESS through a grading system. The grading system assigns "no," "possible," "probable," or "definite" based on the patient's total score and can be found at the RegiSCAR Project website (http://www.regiscar.org). Early recognition and prompt removal of the offending agent is the main treatment for patients with DRESS. Topical corticosteroids and emollients are used for mild cases, and systemic corticosteroids for more severe cases. Full recovery usually takes weeks to months, even after discontinuation of the offending drug. In fact, resolution of the rash in less than 15 days makes DRESS unlikely. Mortality rates range from 5% to 10%, with severe hepatitis being responsible for most deaths.

Patient Course

Based on the RegiSCAR scoring system, our patient was found to have a "definite" case of DRESS syndrome with a score of 6 (2 points for eosinophilia [eosinophil count $>1{,}500/\mu L$ ($1.5 \times 10^9/L$)], 1 point for enlarged lymph nodes, 1 point for atypical lymphocytes, 1 point for rash involving more than 50% of his body, and 1 point for liver involvement). The patient's kidney function remained normal, as did his creatine kinase and lipase levels. He had normal echocardiographic findings and a normal troponin level, and he did not develop respiratory symptoms. Titers and polymerase chain reaction DNA for cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 were obtained on 2 occasions, 3 weeks apart, and were negative for evidence of viral reactivation in this case. The patient was taking carbamazepine and amoxicillin, which are 2 drugs associated with DRESS syndrome. However, carbamazepine was thought to be the offending drug in this case based on the time frame of the rash presentation and was discontinued on hospital admission. Of note, carbamazepine can also cause SJS and TEN. The patient was started on intravenous methylprednisolone, 2 mg/kg per day, which was weaned later to oral corticosteroids. Fluids and electrolytes were monitored closely. His blood culture ultimately grew *S aureus*, likely secondary to his extensive skin inflammation, for which he was treated with vancomycin based on sensitivities of the laboratory for the *Staphylococcus* species. He was discharged after 10 days of hospital stay on a prolonged oral corticosteroid taper. The patient was advised to avoid carbamazepine in the future and was monitored through follow-up care. The rash took 4 months to resolve.

Lessons for the Clinician

- Obtaining a detailed history in patients with prolonged, worsening rash provides insight into potential causative agents.
- Maintain a high index of suspicion for drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in patients who develop skin eruption with eosinophilia 3 to 8 weeks after starting a new drug.
- DRESS syndrome is distinguished from SJS/TEN by morbilliform rash, absence of significant mucosal involvement, and the presence of marked peripheral eosinophilia.
- Immediate withdrawal of the offending drug with continued avoidance in the future is the mainstay of treatment in DRESS syndrome as well as systemic corticosteroids in severe cases. Full recovery typically takes weeks to months.
- Recognizing this syndrome is important as the mortality rate can be up to 10%.

Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/40/2/82.

Case 2: A 13-year-old Boy with a Perplexing Rash

Shafee Salloum and Aphton Lane

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Case 2: A 13-year-old Boy with a Perplexing Rash

Shafee Salloum and Aphton Lane

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Index of Suspicion

3 Gait Instability and Elevated Troponin Level in a 16-year-old Boy

Carrie Johnson, MD,* Shaun Mohan, MD, MPH, CEPS-P†

*Department of Internal Medicine and Pediatrics, and †Department of Pediatrics-Joint Pediatric Heart Care Program, University of Kentucky, Lexington, KY

AUTHOR DISCLOSURE Drs Johnson and Mohan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 16-year-old white boy presents to the emergency department after a fall. He was in the bathroom when he bent over to pick up an object and lost his balance. He fell forward and chipped his front teeth on the bathtub. He admits to feeling light-headed but denies loss of consciousness. Review of systems is positive for a temperature of 100.1°F (37.8°C), headache, rhinorrhea, and chest pain with cough for the previous week.

Vital signs record a temperature of 100.0°F (37.8°C), a pulse of 85 beats/min, a respiratory rate of 18 breaths/min, and blood pressure of 130/67 mm Hg. Physical examination reveals a well-developed, well-nourished, non–toxic-appearing boy with normal cardiopulmonary examination findings. A brief neurologic examination is notable for gait instability and generalized weakness.

Laboratory evaluation shows a normal complete blood cell count and electrolyte levels. An electrocardiogram is significant for normal sinus rhythm, normal axis, ST elevation in anterior leads, and T-wave inversions in anterolateral leads (Fig). Cardiac enzymes are collected and reveal a troponin I level of 7.021 ng/mL (7.021 μg/L) (reference range, 0.00–0.06 ng/mL [0.00–0.06 μg/L]), with normal creatinine kinase and creatine kinase–MB fraction levels. His 2-hour follow-up troponin I level is 6.905 ng/mL (6.905 μg/L). The patient is transferred to a tertiary medical center with a 7-hour troponin T level of 0.053 ng/mL (0.053 μg/L) (reference range, <0.01 ng/mL [<0.01 μg/L]). An echocardiogram reveals normal left ventricle function and size with mild concentric hypertrophy, normal right ventricle size and function, and normal valves. Given his history of viral upper respiratory tract infection and elevated troponin level, there is concern for myocarditis. However, further evaluation reveals an underlying noncardiac diagnosis.

DISCUSSION

Cardiac magnetic resonance imaging was performed to assist in diagnosis. The study revealed hypertrophic cardiomyopathy with severe asymmetrical septal hypertrophy without obstruction, preserved left ventricle systolic function, and normal left ventricle chamber size. The hypertrophy pattern and late gadolinium enhancement pattern were not consistent with amyloidosis, Fabry disease, muscular dystrophy, or myocarditis.

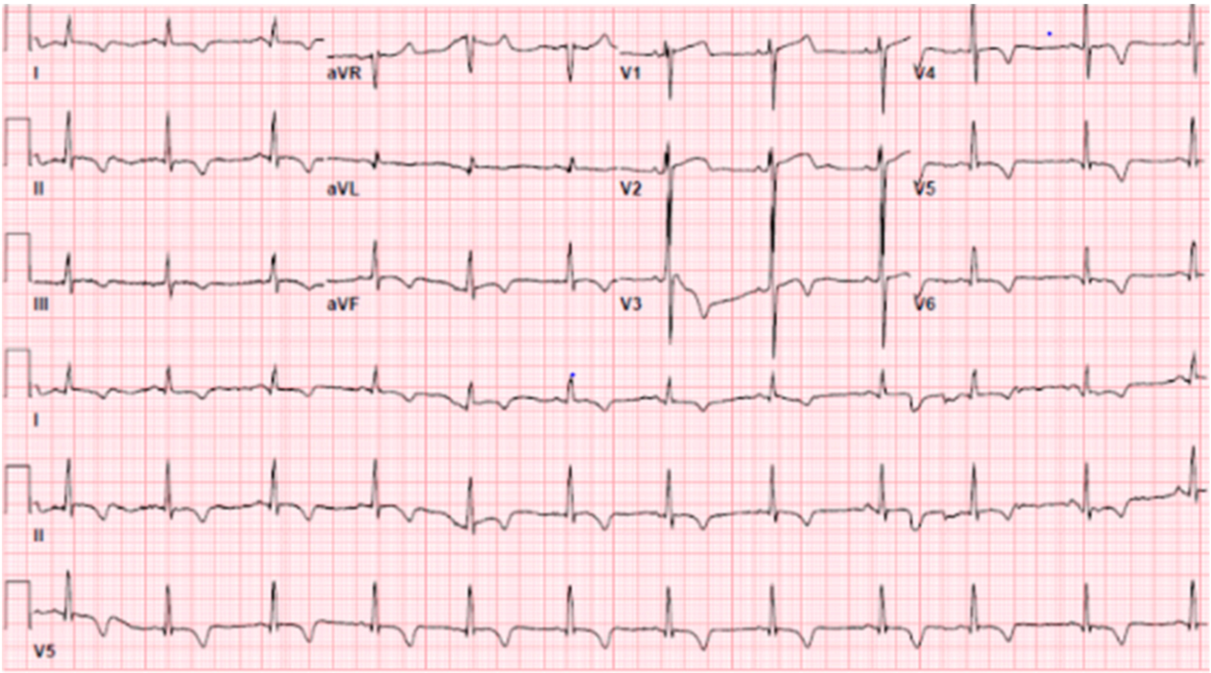

Figure. Electrocardiogram with ST elevations and T-wave inversions.

Further historical investigation revealed that the patient had a "wobbly gait" for the past 2 years. He cannot stand with his feet together and walks with a broad-based gait. He underwent an evaluation in the past that included normal electrolyte, vitamin B_{12}, creatinine kinase, and lactate levels and normal findings on magnetic resonance imaging of his brain. There was no family history of neurologic, muscular, cardiac, or genetic disorders.

A detailed neurologic examination was significant for 1+ bilateral patellar reflexes, up going plantar reflexes bilaterally, clonus at the ankles bilaterally, normal sensation, dysmetria on finger-to-nose and heel-to-shin testing, a positive Romberg sign, wide-based gait, and mild dysarthria.

Given the findings of hypertrophic cardiomyopathy, ataxia, and abnormal neurologic examination findings, there was suspicion for Friedreich ataxia (FRDA). Genetics was consulted, who agreed, and recommended repeated expansion analysis. During follow-up his genetic testing results were positive for 2 alleles with GAA trinucleotide repeat expansion: allele 1 with 1070 GAA repeats and allele 2 with 830 GAA repeats, consistent with diagnosis of FRDA.

The Condition

Friedreich ataxia is a neurodegenerative disorder and is the most common hereditary ataxia. The prevalence of this disease is approximately 1 in 50,000 individuals. It is an autosomal recessive condition with mutation in the frataxin gene on chromosome 9q13. Almost all patients are identified as having an expansion of GAA trinucleotide repeat in intron 1 of 1 or both alleles. Deficiency in the frataxin gene can affect many different organ systems, including the central and peripheral nervous systems, heart, skeleton, or pancreas.

Clinical presentation can vary in affected individuals, pending the extent of GAA expansions. Longer expansions correlate with earlier age at onset and severity of symptoms, including extraneural involvement. Age at onset ranges from 2 years to after 25 years, but the most common age at presentation is in adolescence, with symptoms of limb ataxia, dysarthria, motor weakness, sensory loss, or eventual loss of deep tendon reflexes. Cardiomyopathy may be seen in most patients with FRDA. Patients are frequently asymptomatic, but clinical symptoms include palpitations, dyspnea, arrhythmia, or heart failure. Cardiomyopathy can be detected on ultrasonography or cardiac magnetic resonance imaging. Abnormalities on electrocardiography are commonly identified. Other conditions associated with FRDA include diabetes and spine or foot deformities, such as scoliosis or pes cavus. Not all patients will develop complications in all possible organ systems.

Evaluation and Management

Genetic testing for triplet repeat expansion in frataxin gene in 1 or both alleles confirms the diagnosis. Neuroimaging is recommended to exclude other causes for symptoms (tumor, inflammation, infarct, hemorrhage). Nerve conduction studies typically reveal axonal sensory loss.

Management includes a multidisciplinary approach, including neurology, cardiology, physical and occupational therapy, speech therapy, orthopedics, or endocrinology based on the patient's symptoms and extent of disease. Annual follow-up by cardiology is recommended for monitoring of arrhythmia or heart failure from cardiomyopathy, which is the most common cause of death. An implantable cardioverter defibrillator is indicated for patients with presyncope, syncope, or life-threatening arrhythmias (ventricular tachycardia or fibrillation). There is no specific treatment or definitive cure for FRDA. The condition is progressive and unpredictable. Most patients are wheelchair bound approximately 15 years after onset of symptoms.

Patient Course

The patient's troponin T level peaked at 0.058 ng/mL (0.058 μg/L) and was down trending by the time of hospital discharge; however, it did not normalize. Also, the ST-T–wave changes on his electrocardiogram never resolved. He underwent cardiac catheterization to evaluate coronary anatomy and possible myocardial bridging that would account for his persistent elevated troponin level. Cardiac catheterization did not reveal any abnormalities in his coronary arteries. His cardiac index was normal and had a mildly elevated left pulmonary capillary wedge pressure of 11 mm Hg and no signs of left ventricular outflow tract obstruction. At the time of his procedure, he also had an implantable loop recorder placed to monitor closely for arrhythmias that may account for his symptom of dizziness. During hospitalization, he was monitored on telemetry and there was no evidence of ventricular ectopy or arrhythmias other than occasional premature atrial contractions. His respiratory panel was positive for influenza A H3, which likely accounted for his upper respiratory tract symptoms at the time of admission. He was discharged with outpatient physical therapy services and follow-up with cardiology, neurology, and genetics.

Lessons for the Clinician

- ST-T–wave abnormalities in multiple leads on an electrocardiogram in a child should prompt investigation for structural heart disease as well as possible acquired heart disease.
- Friedreich ataxia can involve nervous system, cardiac, pancreas, or skeletal defects.
- Friedreich ataxia can present with ataxia, loss of deep tendon reflexes, or up going plantar reflexes.
- Patients with hypertrophic cardiomyopathy and focal neurologic signs should raise suspicion of Friedreich ataxia and similar neuromuscular disorders.
- Prompt diagnosis of cardiomyopathy is essential as close monitoring for syncope or arrhythmias can dictate the necessity of implantable cardioverter defibrillator placement.

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Case 3: Gait Instability and Elevated Troponin Level in a 16-year-old Boy

Carrie Johnson and Shaun Mohan

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Index of Suspicion

4 Altered Mental Status in a 6-year-old Boy

Kabelo Thusang, MD,*† Chineyere Onyearugbulem, MD,*†
Jennifer Chao, MD,*† Davor Skaricic, MD*†

*Division of Emergency Medicine, Department of Pediatrics, Kings County Medical Center, Brooklyn, NY
†State University of New York, Brooklyn, NY

AUTHOR DISCLOSURE Drs Thusang, Onyearugbulem, Chao, and Skaricic have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 6-year-old boy presents to the emergency department with a 5-day history of fever, sore throat, and worsening cough. One day before presentation he was found to be difficult to arouse. On the day of hospital admission he is restless and minimally responsive to his mother's commands.

On physical examination his vital signs are normal. He is minimally responsive, does not follow commands, and opens his eyes to noxious stimuli. His neck is supple, with no neck stiffness, and his pupils are 3 mm, symmetrical, and reactive to light. He is uncooperative for a funduscopic examination, and extraocular muscle movements are full and intact, without nystagmus. There is no facial asymmetry, his tongue is midline, and his palate elevates symmetrically with a strong gag response. His power is greater than 3/5 in all muscle groups, with normal tone and bulk. Deep tendon reflexes are 2+ throughout. Toes are down going to plantar stimulation bilaterally.

A blood glucose level, a complete blood cell count, and results of a basic metabolic panel are normal. A routine urine toxicology screen is negative, and acetaminophen and salicylate levels are undetectable. Computed tomography without contrast of the brain shows no acute intracranial hemorrhage, mass effect, or midline shift. Cerebrospinal fluid (CSF) is clear, with a red blood cell count of 19 per μL (0.018×10^9/L) and a white blood cell count of 40/μL (0.04×10^9/L) with lymphocytic predominance (90%). His CSF protein level is 0.02 g/dL (0.20 g/L) and glucose level is 66 mg/dL (3.66 mmol/L); no serum glucose is collected at the same time. A chest radiograph shows no focal consolidation.

Due to concern for sepsis, antibiotic drug therapy is initiated, but the patient's condition continues to deteriorate. He develops bruxism, ankle clonus, a positive Babinski reflex, and nystagmus. Magnetic resonance imaging of the brain with and without contrast does not reveal any abnormality. Electroencephalography shows diffuse cortical slowing without electrographic seizures or epileptiform discharges. Results of CSF polymerase chain reaction (PCR) for herpes simplex virus, enterovirus, West Nile virus, Epstein-Barr virus, cytomegalovirus, adenovirus, and varicella-zoster virus are negative. Bacterial CSF cultures and blood cultures are sterile. Additional laboratory testing reveals the diagnosis.

DISCUSSION

On hospital day 3, serologic testing for *Mycoplasma pneumoniae* immunoglobulin M was markedly elevated (1:2,889) using enzyme immunoassays. Throat PCR results were also positive for *M pneumoniae*. Levofloxacin therapy was initiated at that time, and his condition gradually improved. On hospital day 8, the patient was discharged with levofloxacin to complete a 7-day course. *Mycoplasma pneumoniae* CSF PCR results were negative and CSF cultures were sterile. Three days after discharge he was reexamined in the infectious disease clinic and was found to be back to his baseline and attending school with no restrictions.

The Condition

Encephalitis is the presence of inflammation in the brain parenchyma that is associated with clinical evidence of neurologic dysfunction. Acute encephalitis is a medical emergency with high morbidity and mortality. The clinical presentation includes fever, headache, nausea, vomiting, and altered mental status. *Mycoplasma pneumoniae* has been implicated as one of the commonest causes of encephalitis in children. In the California encephalitis project, *M pneumoniae* was observed to be the most common bacterial pathogen, accounting for 6% of all encephalitis cases. (1) Central nervous system (CNS) manifestations appear in 1 of 1,000 patients with associated *M pneumoniae* infections, (2) including encephalitis, meningitis, myelitis, polyradiculitis, Guillain-Barré syndrome, and peripheral and cranial neuropathy.

The most common presentation in children with *M pneumoniae*–associated CNS disease seems to be encephalitis or meningoencephalitis. In 13 children with *M pneumoniae*–associated neurologic sequelae, 10 presented with encephalitis or meningoencephalitis. (3) In a separate study of patients with *M pneumoniae*–associated CNS disease, 45 of 61 children had encephalitis. (2) Studies have shown *M pneumoniae* encephalitis occurring in pediatric patients of all ages. It remains one of the few treatable causes of encephalitis, but many physicians remain unaware of this, and *M pneumoniae* titers are still not part of the routine evaluation for encephalitis.

Diagnosis

Many patients with *M pneumoniae* encephalitis remain undiagnosed and untreated, thus prolonging morbidity. *Mycoplasma pneumoniae* encephalitis presents similarly to viral encephalitis. Co-infection with other viruses is common, and neuroimaging findings are usually normal. The electroencephalogram frequently shows diffuse slowing indicative of diffuse neuronal dysfunction.

Mycoplasma pneumoniae is difficult to isolate from CSF, and a negative result in CSF, either by PCR or culture, does not rule out the disease. (4) Because CSF studies are low yield, serologic studies of *M pneumoniae* immunoglobulin M or PCR specimens of throat swabs remain an important cornerstone in diagnosis. However, false-positives exist and can make interpretation difficult.

Pathophysiology

The pathogenesis of *M pneumoniae* encephalitis is thought to occur in 2 possible ways. The insult may occur either through direct bacterial invasion or through immunologic-mediated injury. If the prodrome is longer (≥7 days), the etiology is more likely to be immune mediated, whereas if the prodrome is less than 5 days, bacterial neuroinvasion is more likely. Furthermore, if the CSF culture grows *M pneumoniae*, the likely mechanism is through bacterial neuroinvasion. However, the pathogenesis for most cases is an immune-mediated injury due to antigenic similarities between *M pneumoniae* and brain tissue. Antibody-antigen complexes are formed and deposited within small venules in the CNS that causes neurologic injury.

Treatment/Prognosis

Antibiotic drug treatment has been suggested when the prodrome lasts less than 7 days because the likely pathogenesis is bacterial invasion. Case reports have shown improvement with treatment as well as complete neurologic recovery. However, the impact of antibiotic drug therapy has not been well studied. Because of their ability to cross the blood-brain barrier, quinolones or tetracyclines are preferred over macrolides. (4) Intravenous immunoglobulin was efficacious in 1 case when combined with antimicrobial treatment. (5) The prognosis for patients with *M pneumoniae* encephalitis is highly variable, with reports of long-term neurologic sequelae in 48% to 54% of patients with severe developmental delay, seizure disorder, and asymptomatic ventriculomegaly.

Lessons for the Clinician

- When presented with a case of encephalitis accompanied by respiratory symptoms or other extrapulmonary manifestations suggestive of *Mycoplasma pneumoniae* infection, early initiation of treatment with levofloxacin or doxycycline may be beneficial.
- Because the yield of cerebrospinal fluid *M pneumoniae* polymerase chain reaction and culture is low, including *M pneumoniae* titers as a standard test in the evaluation of encephalitis could be advantageous. (5)

References for this article are at http://pedsinreview.aappublications.org/content/40/2/88.

Case 4: Altered Mental Status in a 6-year-old Boy

Kabelo Thusang, Chineyere Onyearugbulem, Jennifer Chao and Davor Skaricic

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in Brief

Pasteurella multocida

Leora Mogilner, MD,* Cynthia Katz, MD*
**Icahn School of Medicine at Mount Sinai, New York, NY*

AUTHOR DISCLOSURE Drs Mogilner and Katz have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Open the mouth of most dogs or cats and you will likely find the bacterium *Pasteurella multocida*. This nonmotile, non–spore-forming, gram-negative coccobacillus is part of normal animal respiratory flora and, therefore, is a common cause of wound infections due to animal bites.

The isolation and description of this organism was first made by Louis Pasteur in 1880, 3 years after it was discovered in birds with fowl cholera. In 1930, Kapel and Holm identified its first true human infection, which was secondary to a cat bite. Further classification of the bacterium over the years ultimately led to the name *Pasteurella multocida* in 1939. *Pasteurella multocida* is a facultatively anaerobic organism that grows on sheep's blood, chocolate, and Mueller-Hinton agar but has no growth on MacConkey medium. It is usually seen as a single bacillus but is sometimes seen in pairs, chains, or clusters. Just 10 minutes of direct exposure to sunlight kills the organism, but it can live in soil for up to 21 days and in water for up to 25 days.

Although *P multocida* can cause serious disease in a variety of animals, this review focuses on human infections. Commonly found in oral or nasal secretions of many animals, including lions, tigers, and buffalo, *P multocida* has been reported in as many as 90% of cats and 50% of dogs. Not surprisingly, human infections generally occur after cat or dog bites, or cat scratches or licks. No food or waterborne illness has been reported. Human-to-human transmission has been reported horizontally via contaminated blood products or from colonized humans via nasopharyngeal secretions, feces, and urine, and vertically from mother to neonate. Respiratory tract infections with *Pasteurella* have been seen in individuals who work with animals or who are involved in the processing of animal tissues.

Dog bites account for 80% to 90% and cat bites account for 5% to 15% of animal bites in the United States. However, only 5% to 10% of dog bites become infected, whereas some series report that up to 50% of cat bites become infected, 6% of which require hospitalization. Children, most commonly boys aged 5 to 9 years, are the victims in most dog bites, whereas adults are more likely to experience cat bites. Dog bites are more likely to present for medical attention and are, therefore, more frequently reported. One study found that 75% of dog bite victims sought medical attention within 24 hours of being bitten, whereas cat bite victims presented only after late complications surfaced. Unlike the slower progression seen with other organisms causing wound infections, the incubation period for bite wound infections with *P multocida* is usually less than 24 hours, and symptoms often progress rapidly. The symptoms noted most commonly are wound site swelling, erythema, tenderness, and discharge and may also include fever, chills, and lymphadenopathy. Complications of *Pasteurella* bite wound infections include abscesses, tenosynovitis, osteomyelitis, and septic arthritis, which may be caused by spread of the soft tissue infection or direct penetration.

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These complications are more likely to occur after cat bites due to the increased likelihood of deep penetration because of the sharpness of cats' teeth.

Clinical manifestations of respiratory infection with *P multocida* are varied and can include pneumonia, empyema, and lung abscess, typically in patients with underlying pulmonary disease or altered immune status. The most common site of infection after the respiratory tract is the abdomen, where appendicitis and peritonitis can be seen. Finally, *P multocida* can cause a variety of disseminated infections, including bacteremia, septicemia, meningitis, endocarditis, and ocular infections. *Pasteurella* bacteremia is more likely in patients with liver disease, organ transplants, and other immunodeficient states, as well as in neonates and the elderly. However, there have been cases of bacteremia reported in previously healthy people. *Pasteurella* infections in neonates, particularly sepsis and meningitis, have been reported after incidental, nontraumatic exposure, usually licking by a pet.

Wound management of animal bites focuses on prevention of infection and begins with obtaining a thorough history and inspecting the wound. Wounds should be vigorously irrigated with normal saline and debrided as necessary, with surgical consultation as needed. It is essential to evaluate for damage to underlying structures, to assess neurovascular integrity, and to determine the need for tetanus or rabies postexposure prophylaxis. The literature presents conflicting recommendations regarding whether closing bite wounds via primary repair, delayed repair, or secondary intention leads to decreased risk of infection and better outcomes. However, certain wounds are considered to be at higher risk for infection and are generally not sutured: cat bites, puncture wounds, minor hand or foot wounds, wounds noted when delay in seeking care (>12 hours), and wounds in immunosuppressed individuals. Primary closure is recommended for facial wounds to optimize cosmetic outcomes. These wounds present a low risk of infection due to adequate blood supply.

Another area of controversy in bite wound care is the use of prophylactic antibiotics. Neither of 2 discrete meta-analyses has provided convincing evidence to recommend antibiotic prophylaxis uniformly. However, antibiotic prophylaxis should be considered for deep cat bites; wounds sutured prematurely; older bites (>8 hours) with evidence of crush injury or edema; wounds with risk of damage to bones, joints, or tendons; bites to the face, hands, and feet; and wounds with early signs of infection. When prescribed, the duration of antibiotic prophylaxis is 3 to 5 days, unless progression of infection indicates longer treatment.

When choosing antibiotics for patients presenting with infections after cat or dog bites, scratches, or licks, it is important to have a high index of suspicion for infection with *P multocida* because many oral antibiotics targeting skin and soft tissue infections will not be effective against this organism. Because many bite wound infections are polymicrobial, it is also imperative that initial treatment cover other bacteria commonly implicated in animal wound infections, including *Staphylococcus aureus, Streptococci*, and anaerobes. Oral amoxicillin-clavulanate and, for severe infection, intravenous ampicillin-sulbactam, piperacillin-tazobactam, and ticarcillin-clavulanate are appropriate choices. For the penicillin-allergic patient, an extended-spectrum cephalosporin and trimethoprim-sulfamethoxazole plus clindamycin are alternatives.

Diagnosis of *P multocida* infection can be made definitively only by culture, either of wound drainage or of other sites of infections, such as cerebrospinal fluid, pleural fluid, or joint fluid. The drug of choice for known *P multocida* is penicillin, but rare β-lactamase–producing strains have been isolated. Oral agents that usually are effective against *P multocida* include amoxicillin, cefuroxime, cefixime, cefpodoxime, doxycycline, and fluoroquinolones. Antistaphylococcal penicillins and first-generation cephalosporins are less effective and, therefore, should not be first-line agents. *Pasteurella* resistance to vancomycin, clindamycin, erythromycin, and aminoglycosides is common. Azithromycin and trimethoprim-sulfamethoxazole may be used as alternatives in penicillin-allergic patients. Depending on allergy history, second- or third-generation cephalosporins should be considered. Once the bacterium has been identified and antibiotic sensitivity is known, the choice of antibiotic can be adjusted accordingly. Local infections are typically treated for 7 to 10 days, and severe infections are treated for 10 to 14 days. Bone and joint infections typically require a longer duration of treatment, often 4 to 6 weeks, and surgical intervention is often indicated.

Given the potential for serious infections due to *P multocida*, teaching families about preventive measures is recommended. Limiting contact with wild animals and proper handling of domestic animals, including preventing pets from licking infants and young children, may help. It is also important to advise families to thoroughly clean bites and scratches and to seek prompt medical attention if the wound shows any signs of infection.

COMMENT: Dog and cat bites are common presentations to health care providers, and the severity can range from trivial to life-threatening. Although prevention is key, I have found it critical to provide good strategies for families with small children to minimize morbidity from dog and cat bites. Yet this can sometimes be difficult as my experience has supported that families love their pets and the comment I frequently hear is that the pet would never hurt their child. Even when a bite has already occurred! As outlined in this thorough *In Brief,* pediatric health care providers need to understand the importance of thorough cleaning of the wounds, knowing when suturing and prophylactic antibiotics are warranted, and assessing the tetanus vaccine status of the patient. In addition, it is important to obtain a history of the animal as to whether owned by the family or a known neighbor, the apparent health of the animal, and whether the attack was provoked as important questions in evaluating for the need for rabies prophylaxis. Consultation with the local health department is warranted for strays or if the animal cannot be recovered because it cannot be observed for 10 to 14 days regarding rabies risk.

– Janet Serwint, MD
Associate Editor, *In Brief*

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Leora Mogilner and Cynthia Katz

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Seborrhea

Olanrewaju O. Falusi, MD*
Children's National Health System, Washington, DC

AUTHOR DISCLOSURE Dr Falusi has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Seborrheic dermatitis (SD) is a common, multifactorial skin disease involving sebaceous areas of the body. It occurs in approximately 10% of the general population, and studies show that up to 70% of infants younger than 3 months experience SD at least once. Although the highest prevalence of SD is at 2 weeks to 3 months of age, the distribution is trimodal, occurring most commonly in infants, then in adolescents, and then in adults older than 50 years. Exposure to maternal estrogen in the newborn period and a surge of androgens in puberty, affecting sebum production, likely contribute to the development of SD. Hair extensions and infrequent hair oil use were significantly related to SD in a study of African American girls. Additional risk factors for SD include immunocompromised status, potentially due to impairments in cellular immunity.

The etiology of SD is unknown, but a variety of hypotheses suggest an interplay of fungal involvement, host inflammatory responses, and several potential risk factors. There is a well-known association between SD and *Malassezia* species, a lipophilic yeast that is normally found in sebum-rich areas of the skin. *Malassezia* yeast has been cultured from 50% of healthy controls, suggesting that SD is not due solely to the presence of the yeast. *Malassezia* species are able to break down skin sebum lipids, producing potentially inflammatory fatty acids, and in response, keratinocytes produce proinflammatory cytokines. Skin biopsy findings include a neutrophilic predominance in the epidermis.

Seborrhea is a clinical diagnosis, and patients may describe the lesions as greasy, yellow, and scaly, most often occurring on the scalp, face, back, chest, and intertriginous areas. Seborrhea is typically asymptomatic or may be mildly pruritic. Particularly in older children and adolescents, the history should include questions to rule out an immunocompromised state, such as asking about frequent infections and failure to thrive. Infants with SD generally present with yellow, oily scales with an erythematous base on the scalp and forehead as "cradle cap," but it may also occur on the nasolabial folds, the postauricular area, or the genitals and other intertriginous areas. Seborrheic dermatitis lesions on the eyelids may present as blepharitis in older children and adolescents. Adolescent boys may also experience SD on facial hair. In dark-skinned people, SD can present as postinflammatory changes such as hypopigmentation. In adults, SD may cause hair loss in the acute phase, but this is rarely permanent. Because SD is a clinical diagnosis, there are no diagnostic tests needed. Skin biopsy can confirm the diagnosis in atypical or refractory cases, but alternative diagnoses and corresponding treatment should be reconsidered before attempting biopsy.

The differential diagnosis includes a variety of skin conditions, and SD is often confused with dermatophyte infections and atopic dermatitis.

Seborrheic Dermatitis: Etiology, Risk Factors, and Treatments: Facts and Controversies. Dessinioti C, Katsambas A. *Clin Dermatol.* 2013;31(4):343–351

Topical Anti-inflammatory Agents for Seborrhoeic Dermatitis of the Face or Scalp. Kastarinen H, Oksanen T, Okokon EO, et al. *Cochrane Database Syst Rev.* 2014;(5): CD009446

Hair Care Practices and Their Association with Scalp and Hair Disorders in African American Girls. Rucker Wright D, Gathers R, Kapke A, Johnson D, Joseph CLM. *J Am Acad Dermatol.* 2011;64(2):253–262

Seborrheic dermatitis can be distinguished from tinea capitis and tinea corporis in its greasy or plaquelike nature and erythematous base, findings less often seen in dermatophyte infections. Atopic dermatitis is less often scaly and more likely to be pruritic and to occur in extensor surfaces. Additional diagnoses may be considered based on the child's age. In infants, SD may have a similar appearance to Langerhans cell histiocytosis (LCH) with erythema and scaling of the scalp; LCH can be differentiated by the pigmentation (often red-brown), lesions (commonly papules and vesicles), and systemic findings, including hepatosplenomegaly. In older children and adolescents, the differential diagnosis should be broadened to include more chronic skin conditions, psoriasis in particular. The scales of SD may be similar to those of psoriasis, but psoriasis typically presents with dark pink or red plaques that are well-demarcated and may be accompanied by pitting and other nail anomalies.

Although SD is usually a self-limited condition in infants, it can distress parents, causing them to seek therapies. For mild cases, applying emollients such as baby oil or petroleum jelly followed by brushing and shampooing may be sufficient. Olive oil is often used, but studies have suggested that organic oils may become a substrate for *Malassezia* species and thereby worsen SD. Frequent shampooing even with nonmedicated shampoo may reduce flaking in mild cases; however, low hair-washing frequency has not been associated with SD in African American girls. Most infant cases respond well to these simple measures. For unresponsive cases, antifungal agents available over-the-counter, such as ketoconazole and selenium sulfide, should be added. Ketoconazole is effective in 1% or 2% formulation, either as a shampoo used twice per week for up to 8 weeks or as a twice-daily gel or lotion used for up to 4 weeks. Selenium sulfide shampoo twice per week may provide relief in 2 to 4 weeks. In infant cases that are refractory to physical measures and antifungal agents, the diagnosis should be reconsidered, and referral to a dermatologist may be warranted.

In older children and adults, physical measures and antifungals, as described, are often used as initial therapies. In addition to selenium sulfide and ketoconazole, ciclopirox antifungal shampoo may be used safely in adults and adolescents 16 years or older. Seborrheic dermatitis can be a chronic, relapsing condition at these ages, and keratolytic or anti-inflammatory medications are recommended for these more severe cases. Keratolytic shampoos such as coal tar and pyrithione zinc are peeling agents that can decrease sebum production and may also have antifungal properties. Salicylic acid shampoo, also available as a lotion, may be used in older children, but its safety and efficacy have not been studied in infants. Corticosteroids have an anti-inflammatory effect in SD and are available in various formulations, including shampoos, ointments, creams, lotions, and foams. Ointments have better skin absorption properties than water-based forms and should be used in more severe or refractory cases. Calcineurin inhibitors such as tacrolimus ointment also reduce inflammation and may be used in children 2 years and older, but use should be limited due to the potential for an increased risk of malignancy. Limited data suggest that tea tree oil shampoo 5% may effectively treat scalp SD. Tea tree oil is generally regarded as safe, but concerns about its estrogenic properties have limited its use.

With these myriad options available to older children and adults, choosing among these medications depends on the patient's age, the severity and distribution of the SD, and tolerance to adverse effects. Generally, treatment typically begins with a trial of physical measures and antifungal shampoos, and stepping up to keratolytics or anti-inflammatories for recalcitrant or recurring cases. However, there is not sufficient evidence to recommend one class of medication over another, as studies have demonstrated similar efficacy among corticosteroids, ketoconazole, and calcineurin inhibitors. Higher-strength corticosteroids have been shown to reduce erythema, scaling, and pruritus more effectively than antifungals, but ketoconazole tends to have fewer adverse effects than corticosteroids and ciclopirox. Adverse effects of either treatment may include skin redness, itching, burning, or hair loss. Corticosteroids available as foams may be preferred in hairy areas due to ease of application. Relapsing cases may improve with intermittent use of medicated shampoos.

Seborrheic dermatitis is generally a benign, self-limited condition that is common particularly in the first year of life. It typically clears by 6 months of age, but treatments can hasten resolution and may be necessary for older children and adolescents. Refractory cases may require longer courses or higher-strength medications, but completely unresponsive cases merit review of treatment adherence, consideration of another diagnosis, evaluation for immunodeficiency, or referral to a dermatologist.

COMMENT: Although I have cared for countless healthy infants with seborrhea, Dr Falusi's *In Brief* reminded me of the high prevalence of seborrhea associated with immunodeficiency conditions in older patients. Multiple treatment options are available that range from over-the-counter options to prescription medications, and the choice of these medications must be balanced with the patient's age along with benefits or potential adverse effects from more aggressive interventions. Primary care providers can diagnose and treat most patients, but for SD cases that are atypical or not responding as you might anticipate to treatment, partnering with a dermatologist can be beneficial.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

Editors' Note

Two perceptive readers submitted an e-letter to the journal expressing concern that the electrocardiogram in the Visual Diagnosis published in the June 2018 issue, "Visual Diagnosis: Syncopal Episode in a 14-year-old Adolescent Boy" (Younes A, Ekeruo IA, Evangelista MS. *Pediatr Rev.* 2018; 39(6): e27-e30, DOI: 10.1542/pir.2016-0150) did not demonstrate the common Brugada presentation (ST elevation in V1 and V2) and that the treatment after one episode of syncope may have been aggressive.

The e-letter and a third-party commentary from Jeffrey J. Kim, MD, Director, Electrophysiology & Pacing, Texas Children's Hospital, can be found online in the "Comments" tab of the Visual Diagnosis article: http://pedsinreview.aappublications.org/content/39/6/e27.comments

The journal is grateful to the readers for sharing their observations and to Dr. Kim for sharing his insights.

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Congestive Heart Failure in Children: 1. A; 2. D; 3. A; 4. B; 5. E.
Novel Drugs of Abuse: 1. C; 2. E; 3. B; 4. E; 5. E.

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Visual Diagnosis

A 19-month-old Girl with a Lumbosacral Mass

Isadore Tarantino, MD,* Rachel Lieberman, MD,* Timothy Zinkus, MD,†
Paul Grabb, MD‡

*Department of Pediatrics, †Department of Radiology, ‡Department of Neurosurgery, Children's Mercy Hospitals and Clinics, Kansas City, MO

PRESENTATION

A previously healthy 19-month-old girl presents for evaluation of an enlarging mass over her lumbosacral region. The child and her family recently immigrated to the United States from Ethiopia, where the girl was born. The girl's mother reports that the mass has been present since birth but was very small at that time. During the subsequent 19 months, the mass has continued to enlarge until it is easily noticeable under her clothing. The girl is reportedly developmentally normal and has no bowel or bladder dysfunction. Her mother is unsure whether the mass is painful because the girl does not cry when she lies on her back. The girl has had no fevers, no overlying redness of the skin covering or surrounding the mass, and no drainage from the mass. Due to inability to receive proper medical care in Ethiopia, she was brought to our emergency department for evaluation of the mass.

On physical examination the girl is thin, but well nourished. The mass is entirely covered by skin and sits midline over the lumbosacral region. It measures approximately 7×6×4 cm (Fig 1). The mass is mobile and fluid-filled, with only minimal tenderness to palpation. There is no overlying skin discoloration, and no abnormal cutaneous markings. The girl demonstrates the ability to walk normally, with appropriate lower-extremity muscle tone and intact lower-extremity sensation.

Initial ultrasonography performed in the emergency department reveals a large, irregular, cystic structure in the subcutaneous tissue with a tail extending deeper toward the spine. The girl is admitted to the hospital for further evaluation, and magnetic resonance imaging (MRI) reveals the diagnosis.

DIAGNOSIS

The MRI of the brain and total spine demonstrates dorsal extension of the meninges into the overlying soft tissues and protrusion of the neural placode, an embryologic structure, into that space (Fig 2). Fat is noted to be present along the dorsal aspect of the distal spinal cord and in the meningocele (Fig 3). Given all of these elements, a diagnosis of lipomyelocystocele with spinal dysraphism is made.

DISCUSSION

Lipomyelocystocele is a variant of lipomyelomeningocele, and both represent specific types of closed neural tube defects known as occult spinal dysraphism.

AUTHOR DISCLOSURE Drs Tarantino, Lieberman, Zinkus, and Grabb have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

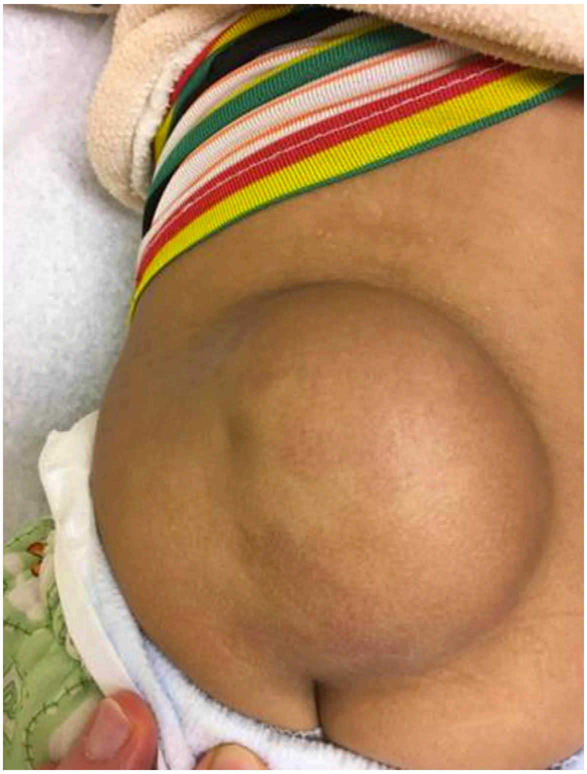

Figure 1. Midline lumbosacral mass measuring approximately 7×6×4 cm.

Spinal dysraphism, also known as spina bifida, refers to defective closure of the vertebral column and represents a group of congenital anomalies of the spinal cord. These defects are subdivided into 2 distinct syndromes: 1) spina bifida cystica, which are more widely recognized lesions, including meningocele and myelomeningocele, and 2) spina bifida occulta, which includes lipomyelomeningocele lesions.

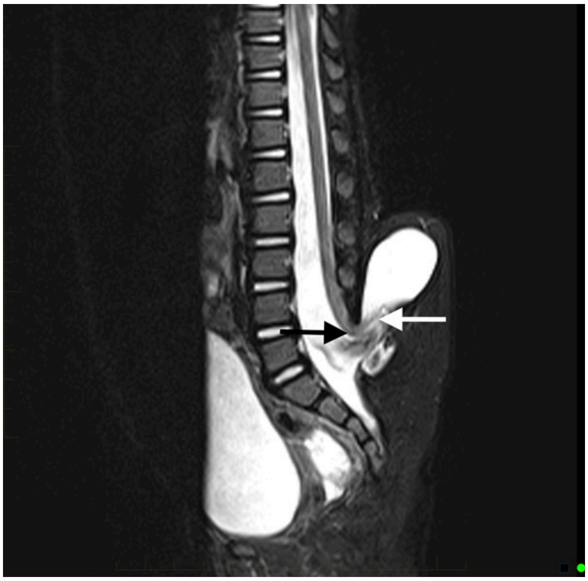

Figure 2. The T2-weighted sagittal magnetic resonance image shows the spinal cord low-lying at the level of L5-S1, with the dysraphic defect demonstrated by the black arrow. The neural placode (white arrow) can be seen protruding into the meningocele.

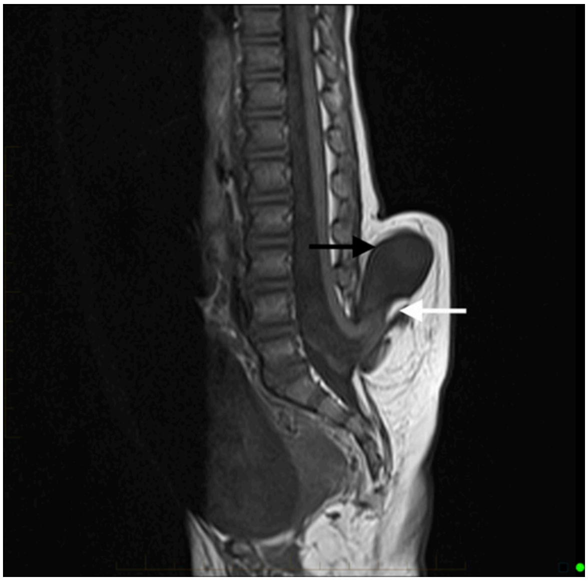

Figure 3. The T1-weighted sagittal magnetic resonance image illustrates the lipoma (white arrow) positioned in the meningocele along the dorsal aspect of the spinal cord. The black arrow shows the confined cyst, walling off the surrounding subcutaneous fat.

Spina bifida cystica lesions are characterized by herniation of the meninges, spinal cord, or both through a defect in the skin. Meningoceles are lesions in which the protruding sac contains only meninges, myeloceles are lesions in which the protruding sac contains only spinal cord, and myelomeningoceles contain both meninges and spinal cord. These lesions are apparent at birth and often easily visible on prenatal ultrasonography. Prenatally, an elevated α-fetoprotein level can also suggest this diagnosis. Children with spina bifida cystica lesions commonly have hydrocephalus because many have a concurrent Chiari type II malformation. Other associated symptoms include varying degrees of sensation and paralysis below the level of the lesion, orthopedic complications with atrophy of muscles due to lack of nerve innervation, and urologic abnormalities, the most common being neurogenic bladder.

Spina bifida occulta lesions are distinct in that they have no exposed neural tissue and are always covered by skin. Children with these lesions often have associated lipomas (lipomyelomeningocele) and tethering of the spinal cord. Lipomyelomeningocele has been found to be the most common cause of congenital tethering in patients with spina bifida occulta and has been reported to account for up to half of all occult spinal dysraphisms and 20% of lumbosacral masses. Lipomyelocystocele is distinct from lipomyelomeningocele because of the cystic component associated with this lesion. Lipomyelocystocele has been reported to account for approximately 5% of skin-covered lumbosacral masses.

Lipomyelocystocele and lipomyelomeningocele lesions are not always present at birth, but typically become apparent with time. Common physical examination findings include a midline, skin-covered, fluid-filled, lumbosacral mass. There can be associated cutaneous markings, including hair, nevi, or tags. Many newborns with these lesions do not have neurologic, orthopedic, urologic, or anorectal symptoms. However, progressive neurologic deterioration is known to occur at any age and can even go undetected into adulthood before back pain and other neurologic symptoms occur. Some infants, however, have precipitous loss of function early in life that coincides with rapid enlargement of the lipomyelocystocele. The symptomatic deterioration seen in older patients is thought to be secondary to the tethered cord, which causes stretching of the spinal cord with subsequent ischemia and hypoxia to the cord and sacral nerve roots. Patients with spina bifida occulta lesions rarely have associated hydrocephalus, gyral anomalies, or Chiari malformations. It has been suggested that the cognitive impairments that can occur in children with myelomeningocele do not occur in children with lipomyelomeningocele.

Diagnosis requires radiographic imaging; MRI is preferred over ultrasonography given its greater sensitivity, specificity, and overall enhanced contrast resolution.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for these lesions is limited but should include other occult spinal dysraphisms, including hypertrophied filum terminale, congenital dermal sinus, neurenteric cyst, myelocystocele, sacral agenesis diastematomyelia, and anterior sacral meningocele. These entities become symptomatic by spinal cord tethering but may also become apparent due to recurrent episodes of meningitis or spinal abscesses. This is especially true of congenital dermal sinuses, which are often detected by recurrent meningitis or superficial skin infections. Other considerations in the differential diagnosis of lumbosacral masses should include myelomeningocele or meningocele, especially when the lesion is not skin-covered, if the child is older, and when neurologic deficits exist. An intraspinal teratoma or cystic hygroma may also present with similar clinical pictures, although it can easily be distinguished on imaging, particularly the teratoma with its multifarious components, such as bone, cartilage, and fat.

MANAGEMENT

Traditionally, management included postponement of surgical intervention until the patient demonstrated neurologic deterioration. However, reports showed that this led to an 80% rate of permanent neurologic dysfunction. Now, management in most centers includes early surgical exploration in all children with skin-covered lumbosacral masses, preferably in infancy. Some still dispute the value of prophylactic surgery before the development of neurologic symptoms; however, early intervention remains the standard of care because of the risk of neurologic deterioration known to eventually occur with these lesions. This is particularly true regarding bladder function because surgery often cannot resolve bladder function back to normal levels once there has been urologic compromise. Thus, before surgery, it is recommended to perform a urologic evaluation, including ultrasonography of the bladder and urodynamic studies.

Surgical goals include debulking of the lipoma to relieve compression and, importantly, untethering of the spinal cord to prevent neurologic deterioration. The dural canal must then be reconstructed to prevent CSF leakage, often requiring a dural graft. Follow-up imaging is indicated if neurologic function changes or postoperative infection is suspected.

PROGNOSIS

The most common complications after surgery include CSF leaks, wound breakdown, and deterioration in function. However, multiple studies have found no correlation in deterioration between patients who were symptomatic before surgery and those who were asymptomatic. One study did examine retethering of the spinal cord after tethered cord repair and reported a 3.3% increase per year in retethering requiring repeated surgery. However, multiple case series have found that intervention maintains or improves function in patients who were symptomatic before surgery.

PATIENT COURSE

The girl remained clinically stable during her initial hospital admission and was discharged with follow-up in the neurosurgery clinic. She ultimately underwent surgical repair of the lipomyelocystocele and release of the adjacent tethered cord with debulking of the subcutaneous lipoma. She tolerated the procedure well and recovered with preserved neurologic function. However, the girl was readmitted 1 week later for a postoperative wound infection. This required washout of the previous incision and a prolonged antimicrobial drug course, but she recovered fully and continued to be followed closely by neurosurgery.

Summary

- Spina bifida occulta lesions are distinct entities in that the neural elements are completely covered by skin, and lipomyelocystocele and lipomyelomeningocele should be considered in the differential diagnosis of a skin-covered midline mass.
- Radiographic imaging remains the standard for diagnosis, with magnetic resonance imaging being preferred over ultrasonography given its ability to better differentiate the elements required for diagnosis.
- Early surgical intervention remains the standard of care to prevent the neurologic dysfunction that can occur with these lesions.

Suggested Readings

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Shabana Yusuf, *Houston, TX*

PUBLISHER: American Academy of Pediatrics
Mary Lou White, Chief Product Officer/Senior Vice President, Membership, Marketing and Publishing
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Heat-Related Illness in Children in an Era of Extreme Temperatures

Courtney W. Mangus, MD,* Therese L. Canares, MD*

**Division of Pediatric Emergency Medicine, Department of Pediatrics, Johns Hopkins University, School of Medicine, Baltimore, MD*

Practice Gap

1. It is important for clinicians to understand the increasing incidence of heat-related illnesses and their implications on children.
2. Clinicians should be able to recognize the difference between heat exhaustion and heat stroke.
3. Clinicians should learn how to implement rapid cooling in the treatment of heat stroke.

Objectives

After completing this article, readers should be able to:

1. Distinguish between heat exhaustion and heat stroke.
2. Recognize risks and behaviors associated with heat-related illness.
3. Effectively diagnose and treat heat stroke.
4. Identify effective prevention strategies for both exertional and nonexertional heat stroke.

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ABBREVIATIONS

AMS	altered mental status
CNS	central nervous system
CTM	critical thermal maximum
HRI	heat-related illness
WBGT	wet bulb globe temperature

INTRODUCTION

A 12-year-old obese football player finishes his second 2-hour practice on a hot August day. His temperature is 105°F (40.6°C), and he is agitated and confused. His family calls you, his general pediatrician, seeking guidance. What advice do you give?

A bystander discovers a 23-month-old infant in the back seat of a minivan on a warm day. She is flushed, fussy, and has vomited. The baby is brought to your community emergency department for further management. What are your next steps?

As the planet gets warmer, the incidence of heat-related illness (HRI) and injury is increasing. (1)(2)(3)(4)(5) Among those suffering HRI, children compose almost half (47.6%) of this population. (1) In the pediatric population, the most common forms of heat-related pathology occur in exercising adolescents and in children left unattended in vehicles or excessively warm environments. Pediatricians must effectively counsel caregivers in recognizing the dangers related to heat exposure and preventing dehydration and HRI. When prevention fails, prompt recognition and treatment of HRI become paramount.

DEFINITIONS AND TERMINOLOGY

Heat-related illness refers to a clinical spectrum of disorders resulting from exposure to excessive environmental heat and the body's inability to effectively regulate heat. Presentation can range from mild (heat rash, heat stress) to severe (heat stroke). Note that tolerance to heat varies by individual. Many factors, including general health, overall conditioning, hydration status, and ability to acclimatize (or adapt over time to change in temperature) play a role in the effect that heat has on the individual.

Heat rash and *prickly heat* are colloquial names for miliaria. It is commonly seen in infants during periods of high heat and humidity. It is an erythematous, papular, or vesicular rash caused by the obstruction of eccrine sweat glands. (6) It may be pruritic and is benign and self-limited. Treatment is supportive and includes wearing light, loose garments and avoiding overheating. (7)

Heat edema is a mild form of HRI manifested as swelling of the feet, hands, and other dependent areas. It occurs in unacclimatized individuals as a result of vasodilation and venous pooling. (6) Although more common among the elderly, heat edema can occur in children as well. The body temperature of the individual is normal and the condition is unrelated to heart failure or kidney disease. Treatment is supportive: elevation, compression stockings, and moving to a cooler environment. (7)

Heat cramps are due to involuntary contractions of skeletal muscle that occur during or after exercise. (8)(9) The term *heat cramps* is a misnomer because the heat does not directly trigger cramping, and high-intensity exercise in cold environments (eg, hockey, swimming) can be associated with cramps. A more accurate term is *exercise-associated muscle cramping*. The spasms are painful and usually involve only the muscle groups actively involved in exercise. (8) They typically occur in the dehydrated, deconditioned, or poorly acclimatized athlete. (10) Risk factors include a history of muscle cramps or previous injury to the muscle, tendon, or ligament; heavy sweating; dehydration; or poor sodium intake before or during exercise. (9) Treatment is supportive: rest, hydration, and static stretching. (6)(8)(9)

Heat syncope is also related to vasodilation and venous pooling. It is an orthostatic event that causes brief loss of consciousness and is usually seen in an individual who is standing for a prolonged period or changing positions rapidly in a warm environment. (8) Heat exposure may contribute to the event but is not the causative factor. As with heat edema, body temperature is normal. Treatment is also similar: individuals should be moved to a cooler environment and remain supine until light-headedness has resolved and vital signs have normalized. Hydration status should be assessed while providing the patient with oral or intravenous fluids. (1)

Heat stress represents a mild form of HRI. It refers to perceived discomfort and physical strain that result from exposure to heat or a warm environment. Symptoms are typically mild, and core temperature remains within the normal range. (7)

Heat exhaustion (also called *heat injury*) is a moderate illness associated with increase in core temperature (98.6°F–104°F [37°C–40°C]) and symptoms include thirst, headache, weakness, syncope, vomiting, and dizziness. (6) Heat exhaustion is often accompanied by dehydration and heavy sweating. The patient's vital signs will likely demonstrate tachycardia and hypotension. An important feature of this clinical syndrome is that there is no central nervous system (CNS) dysfunction or end-organ damage. (9) If there are CNS symptoms (headache, slight confusion), they are mild and resolve quickly with cooling and rest. (7)

Treatment of heat exhaustion entails cessation of physical exertion, removal of excess clothing and equipment, movement to a cooler environment, and hydration with oral or intravenous fluids. (1) Cooling methods may include taking a cool shower or applying cold compresses. Heat exhaustion may progress to heat stroke if not recognized and managed promptly. (6) When treated promptly and appropriately, however, most patients' symptoms will resolve quickly, and hospital admission is unnecessary. (8)

Heat stroke represents the most severe form of HRI and results from thermoregulatory failure. It is a life-threatening condition defined as a core temperature greater than 104°F (>40°C) accompanied by CNS dysfunction in the setting of known heat exposure and/or strenuous exercise. The CNS abnormalities can include agitation, confusion, delirium, or coma. Henceforth, this review focuses on the differential diagnosis, pathophysiology, etiology, diagnosis, management, and prevention of heat stroke.

DIFFERENTIAL DIAGNOSIS

It is important for the clinician to be aware of and distinguish other causes of hyperthermia. Hyperthermia in the form of a fever is a common occurrence in the pediatric population. A fever is a normal physiologic response to infection or inflammation that causes a rise in body temperature. The response is controlled by central thermoregulatory centers in the brain, and the temperature rises, although not usually higher than 105.8°F (41°C), in a neurologically normal host. Fever is often, but not always, accompanied by other signs of infection, illness, or inflammation.

Less common causes of hyperthermia include neuroleptic malignant syndrome and malignant hyperthermia. Neuroleptic malignant syndrome is a life-threatening, idiosyncratic reaction in patients taking antipsychotic medications. It is characterized by the clinical triad of hyperthermia, muscle rigidity, and altered mental status in the setting of exposure to dopaminergic agents. Malignant hyperthermia is an inherited condition that occurs in susceptible individuals exposed to inhalational anesthetics and/or succinylcholine. It is characterized by hyperthermia and skeletal muscle rigidity and responds to treatment with dantrolene. (11)

PATHOPHYSIOLOGY

Human body temperature is regulated by the anterior hypothalamus and is maintained within a narrow range of 97.7°F to 99.5°F (36.5°C–37.5°C). (8) As the body's core temperature begins to rise (through exercise or exposure to ambient heat), the body shifts from heat storage to heat dissipation. (10) The body has several processes by which it can thermoregulate, although these processes become increasingly ineffective as ambient temperature increases.

Radiation of heat from the body to the environment will occur only if the ambient temperature is below the body temperature. Convection occurs when heat from the body is transferred to cooler air (gas), and conduction occurs when heat is directly transferred from a warmer surface (the body) to a cooler one. Thus, as ambient temperature increases, the primary method of thermoregulation is evaporation. (10) Sweat is vaporized at the skin surface, allowing heat dissipation and cooling.

Physiologic changes occur as the core body temperature increases: vasodilation leads to increased heart rate, stroke volume, and cardiac output. Warmer blood moves peripherally to the skin, allowing for sweat production and evaporation. (10) As blood moves from the core to the periphery, visceral perfusion is diminished, most prominently in the kidneys and gut. (2) If exposure to heat is excessive or prolonged, the body is less able to compensate.

The critical thermal maximum (CTM) reflects the core body temperature and duration of heat exposure that is lethal to an animal. In humans, the CTM is estimated to be 106.9°F to 107.6°F (41.6°C–42°C) for 1 to 8 hours. (12) Prolonged hyperthermia exceeding the CTM can lead to a dangerous cascade of ischemia, end-organ damage, multisystem organ failure, and potentially death.

As the body attempts to cool, high demand on the heart can progress to high-output cardiac failure and cardiogenic shock. Hypotension often develops and is multifactorial. It is commonly due to vasodilation (as part of the thermoregulatory process) as well as hypovolemia (secondary to profuse sweating and insensible losses). In the most severe cases, hypovolemia may also be secondary to cardiogenic shock. Prolonged hypotension will ultimately lead to poor perfusion, ischemic injury, and end-organ damage. In addition, the vascular endothelium is sensitive to heat, and excessive exposure may result in disseminated intravascular coagulation. As vascular and mucosal permeability is altered, cerebral and gut edema may develop. (2)(11)

On the cellular level, protective mechanisms against hyperthermia exist; however, exposure to extreme or prolonged heat will result in direct cytotoxic effects to cells as well as activation of various cytokines and inflammatory pathways. Protein denaturation and programmed cell death (apoptosis) will ultimately occur. (2)(11) Because hyperthermia can be life-threatening, it is important for clinicians to understand the thermoregulatory process and the manner in which age and development effect it.

AGE AND THERMOREGULATION

It had previously been suggested that pediatric athletes were less capable of effective thermoregulation during exercise; however, newer findings demonstrate this to be false and suggest that, from a physiology standpoint, young athletes are not more susceptible to heat injury. (13) In fact, children are generally not at higher risk for HRI than adults (who tend to have more cardiovascular disease and comorbidities that worsen HRI outcomes). However, there are physiologic and developmental differences unique to children regarding thermoregulation.

Children and adolescents take longer to acclimatize to a warm environment than adults. Acclimatization is the process by which an individual adapts to a change in temperature and/or humidity. Physiologic changes that occur during the acclimatization period include increased sweat production, reduced electrolyte losses in sweat, increased skin blood flow during exercise, larger stroke volume, larger plasma volume, increased aldosterone production with decreased urine sodium excretion, and decreased temperature threshold to start sweating. (8)(10) Student athletes should be given 10 to 14 days to acclimatize to new exercise in warm weather. (14) Furthermore, infants and young children are thought to have less effective thermoregulation than adults plus lack developmental capabilities to change their behavior in response to overheating (eg, drink water, remove seat belts or clothing, change environments). (15) Special care must be given to their unique needs during periods of extreme heat.

ETIOLOGY AND RISK FACTORS

Exposure to heat is the primary etiology of heat stroke. The nature of the exposure allows for further classification of heat stroke into nonexertional (classic) and exertional heat stroke. Nonexertional heat stroke results from exposure to high environmental temperatures in the absence of excessive physical activity. It is most commonly seen with extremes of age (young children and the elderly are at highest risk) during heat waves or extreme heat events. Common scenarios include a child left unattended in a vehicle (vehicular heat stroke) or living in a dwelling without central air-conditioning or climate control. (16) During extreme heat events, air-conditioning has been shown to be a protective factor and is associated with decreased risk of heat-related mortality. (17)(18)

In the pediatric population, vehicular heat stroke is not uncommon, with an average of 37 deaths due to vehicular heat stroke per year in the United States during the past 2 decades. Of these vehicular heat stroke deaths, 87% were in children younger than 3 years. (19) A review of 171 deaths from vehicular heat stroke found that fatalities were attributed to children playing in the vehicle (27%) or to children left in the vehicle (73%). (20) In the most common scenario, a parent forgets that the child is in the back of the car and unintentionally leaves him or her in the vehicle. This conceivably happens when a parent deviates from their daily routine. (21)(22) A parent who usually drives straight to work may, on a different day, take his or her infant to day care and then drive to work. Out of habit or absentmindedness, the parent may follow his or her typical routine and go straight to work, leaving the infant in the vehicle unintentionally. In other circumstances, poorly supervised young children may gain access to an unattended vehicle and risk entrapment when they cannot escape from the trunk or vehicle. Finally, a parent may intentionally leave a child unattended in a car not realizing that even short periods in a closed vehicle may cause a serious HRI. (20)(22)

It is an all-too-common misconception that vehicle-related HRI can happen only on extremely warm days. In reality, vehicles trap heat from the sun, causing the temperature within the car to rise rapidly. Even on days where the outdoor temperature is mild but sunny, the interior of the vehicle can reach dangerous temperatures. One study demonstrated these findings: on a day with an ambient temperature of 72°F (22.2°C), the interior of a car can reach 117°F (47.2°C) within 60 minutes. Furthermore, 80% of the temperature rise occurs in the first 30 minutes. (15) Cracking the car's windows does little to alter this effect. Thus, children should not be left alone in cars, even with the windows open. (21) In fact, at the time of this writing, 19 of the states in the United States have made it illegal to leave a child unattended in a vehicle. (23)

In contrast to nonexertional heat stroke, exertional heat stroke is most common in the athlete and occurs after prolonged strenuous exercise. It may also be seen in military recruits, public safety workers, and manual laborers who work in warm environments, often in uniforms or heavy protective gear.

It is estimated that more than 9,000 high school athletes are treated for exertional heat illness each year. (3) Football players are at highest risk for exertional heat stroke among athletes. (3) Between 1995 and 2010, an average of 2 high school football players died annually of exertional heat stroke. August is the most common month for exertional heat illness to occur, although athletes can be affected during cooler months as well. (3)(4)(11) August has an especially high incidence of HRI, in part due to high temperatures and in part due to adolescent athletes entering preseason sports (and lacking acclimatization) after becoming deconditioned over the summer.

Conditions such as obesity, sickle cell disease and trait, cystic fibrosis, and diabetes (mellitus and insipidus) can put adolescents at higher risk for experiencing HRI. (6)(10)(24) Also, drugs that decrease sweating (anticholinergics, phenothiazines), increase fluid loss (diuretics, alcohol), or increase heat production (sympathomimetics) may adversely affect thermoregulatory capabilities. (8)(10) Last, being generally deconditioned, being dehydrated, or recovering from a recent illness are all risk factors for exertional heat illness. Primary care pediatricians, sports medicine physicians, coaches, and athletic trainers should be aware of pediatric athletes' risk factors to target preventive measures against HRI.

DIAGNOSIS

Heat exhaustion and heat stroke are clinical diagnoses, both defined by hyperthermia after heat exposure. Recall that significant CNS dysfunction (ie, altered mental status) and core body temperature higher than 104°F (40°C) are what differentiate heat stroke from heat exhaustion. Regardless of the type of exposure, victims of exertional and nonexertional heat stroke will usually present with similar clinical findings; however, victims of heat stroke may also have evidence of end-organ damage. Clinical findings of heat stroke and heat exhaustion are summarized in Fig 1.

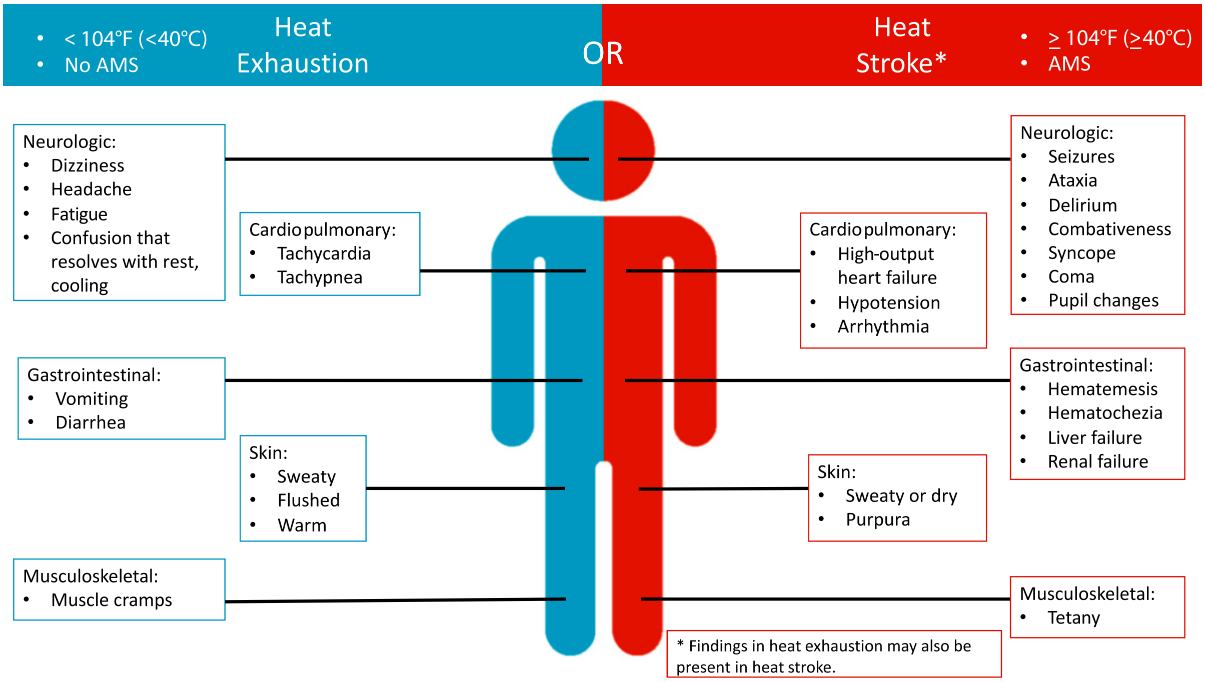


Figure 1. Clinical findings in heat exhaustion or heat stroke. AMS=altered mental status.

The CNS symptoms may begin as mild confusion but become severe (eg, delirium, seizures, encephalopathy, coma) and more apparent once core temperature is greater than 105.8°F (>41°C). It is important to remember that core temperature on presentation to medical care may be less than 104°F (<40°C) if cooling measures have already been initiated. Therefore, heat stroke should remain on the differential diagnosis for patients with the right exposure and clinical presentation even if core temperature is less than 104°F (<40°C). (6)(7) In terms of skin findings, patients with classic or nonexertional heat stroke will have hot, dry skin secondary to prolonged thermoregulatory dysfunction. (8) In contrast, patients with exertional heat stroke may have cool, clammy skin or be warm and diaphoretic if they were engaged in exercise or strenuous activity immediately before presentation. (25)

MANAGEMENT

Heat stroke must be recognized promptly and treated aggressively. Treatment is summarized in Table 1. Resuscitation begins first and foremost with rapid assessment of the patient's airway, breathing, and circulation per life-support protocols (with simultaneous emergency medical services activation depending on the site of presentation). Measurement of core temperature and initiation of cooling should be the next priority once the airway, breathing, and circulation have been addressed. Rectal thermometers are the gold standard to assess core body temperature. (9)(25) External commercial thermometers that assess body temperature tympanically, orally, or temporally are not reliable to assess core temperature and should not be used in place of a rectal thermometer. (8)

Cooling

Cooling must begin as soon as heat stroke is suspected. (25) The purpose of cooling is twofold: to return blood flow from the periphery to the core and to lower body temperature by reducing the body's hypermetabolic state. (9) The method of cooling will depend on the resources available and, potentially, the age of the patient. First, all clothing and equipment (sweaty garments, athletic gear, uniforms) should be removed while cooling is initiated and the child is moved to a shaded area.

For older children and athletes with exertional heat stroke, current data suggest that cold-water immersion (eg, in ice water or an ice bath) is the optimal and most effective cooling method. (9)(26)(27)(28)(29)(30) This can be initiated on-site, if available. Water temperature should be less than 60°F (<15°C), and the water should be continually circulated or stirred. The patient's body should be fully immersed when possible except for the head and neck (which can be covered by a wet towel). (25) If medical personnel are present, vital signs and temperature should be monitored frequently (eg, every 3–5 minutes). (9) For

TABLE 1. **Treatment Recommendations for Heat Stroke**

PREHOSPITAL CARE
∘ Assess the airway, breathing, and circulation
∘ Measure core body temperature (rectal)
∘ Remove clothing and athletic equipment
∘ Older (cooperative) child or adolescent:
■ Cold-water immersion (if available), cover head/neck with wet towel
∘ Infants, young child, or immersion not available:
■ Evaporative cooling with wet towels or sheets and high-flow fan
∘ Repeat assessment of temperature and vital signs every 3–5 min
∘ Initiate hospital transfer[a]
EMERGENCY DEPARTMENT CARE
∘ Assess the airway, breathing, circulation, and (neurologic) disability
■ Consider intubation if unable to protect airway
■ Consider benzodiazepines for combativeness, seizures, or excess shivering
∘ Measure core body temperature (rectal)
∘ Remove clothing and athletic equipment
∘ Apply cardiorespiratory monitor and rectal or esophageal temperature probe
∘ Establish vascular access, evaluate for associated complications
∘ Evaporative cooling with wet towels or sheets, water spray, high-flow fan, cooling blanket
∘ Normal saline bolus (at room temperature)
∘ Repeat assessment of temperature and vital signs every 3–5 min
∘ Continue cooling until core temperature is ≤102°F (≤38.9°C)
∘ Expectant management of end-organ damage and complications

[a] *If a physician is on-site and symptoms improve immediately, hospital transfer may be at the discretion of the physician. (7)*

athletes with exertional heat illness, it is recommended to cool first and transport second when feasible. (9)(25) If effective on-scene cooling cannot be achieved (or if the patient has other complications necessitating immediate emergency department management), transfer should be initiated promptly, although available cooling methods should be used en route. (25)

In infants and younger children, there are limited data regarding immersive cooling, and concerns have been raised about patient cooperation and safety regarding reflex bradycardia. (31)(32) In this population, some experts recommend evaporative cooling rather than cold-water immersion. Evaporative cooling should be used for young children or for older children when cold-water immersion is unavailable. Evaporative strategies include spraying the patient with lukewarm water while using fans to maximize air circulation.

Other methods for both young and older children may include application of cold, wet towels (which should be continuously resoaked and reapplied) or placing the patient in a cold shower. Ice packs to the axilla or groin have been shown to be only marginally effective and should be used only if there are no available alternatives. (8) The goal of cooling is to rapidly lower the core temperature while aiming to prevent overshoot hypothermia. The recommended threshold to stop cooling varies in the literature and ranges from 101.5°F to 102°F (38.6°C–38.9°C). (8)(10)(25)(28) Throughout the process, core temperature should be continuously monitored via a rectal or esophageal probe. (10) Other vital signs and mental status should also be continuously assessed. There are currently insufficient data to definitively recommend cooling with chilled intravascular fluids or gastric, rectal, bladder, or peritoneal lavage.

Additional Evaluation and Management

With the airway, breathing, and circulation addressed and cooling underway, secondary management includes assessment of hydration status and electrolytes as well as identification and treatment of any complications of heat stroke. Complications of heat stroke and associated diagnostic evaluation are summarized in Table 2. Evaluation should include identification of end-organ damage. (2)(6)(7)(10)(11)

Fluid Management

An indwelling bladder catheter may be used for accurate and continuous urine output measurements. (10) Rate and type of rehydration fluid should be guided by the patient's volume status, hemodynamic state, and any identified electrolyte imbalance. Patients in shock will require rapid administration of isotonic fluid. Most patients should be given a 20-mL/kg fluid bolus and then reassessed.

Medications

There are no specific medications indicated in the treatment of heat stroke. Antipyretics are not useful in lowering core temperature due to HRI. Similarly, dantrolene, which is used to treat malignant hyperthermia, has no role in the management of heat stroke. (11) Pharmacotherapy may be indicated in managing the complications of heat stroke and should be considered on a case-by-case basis. For example, benzodiazepines may be administered to help control the shivering mechanism and to prevent seizures, which may be a complication of heat stroke. (10)

OUTCOMES

The morbidity and mortality of heat stroke are incompletely characterized, although it is known that outcome is directly related to how quickly cooling is initiated. (10) It is also known that severity of the initial injury is related to the duration of hyperthermia and the height of the temperature. (11) Patients with mild heat stroke generally make a full recovery with normal neurologic function. Patients with severe heat stroke may survive but with permanent neurologic injury. (11) It is estimated that up to one-third of patients with severe heat stroke have permanent moderate or severe neurologic impairment and a mortality rate of at least 10%. (11) Poor prognostic signs include hemoptysis, hematuria, gastrointestinal bleeding, and conjunctival hemorrhage. (10) Patients with higher initial temperatures, hypotension, or low Glasgow Coma Scale scores (<12) are more likely to die, (33) and death is usually from cardiovascular collapse. (10)

PREVENTION

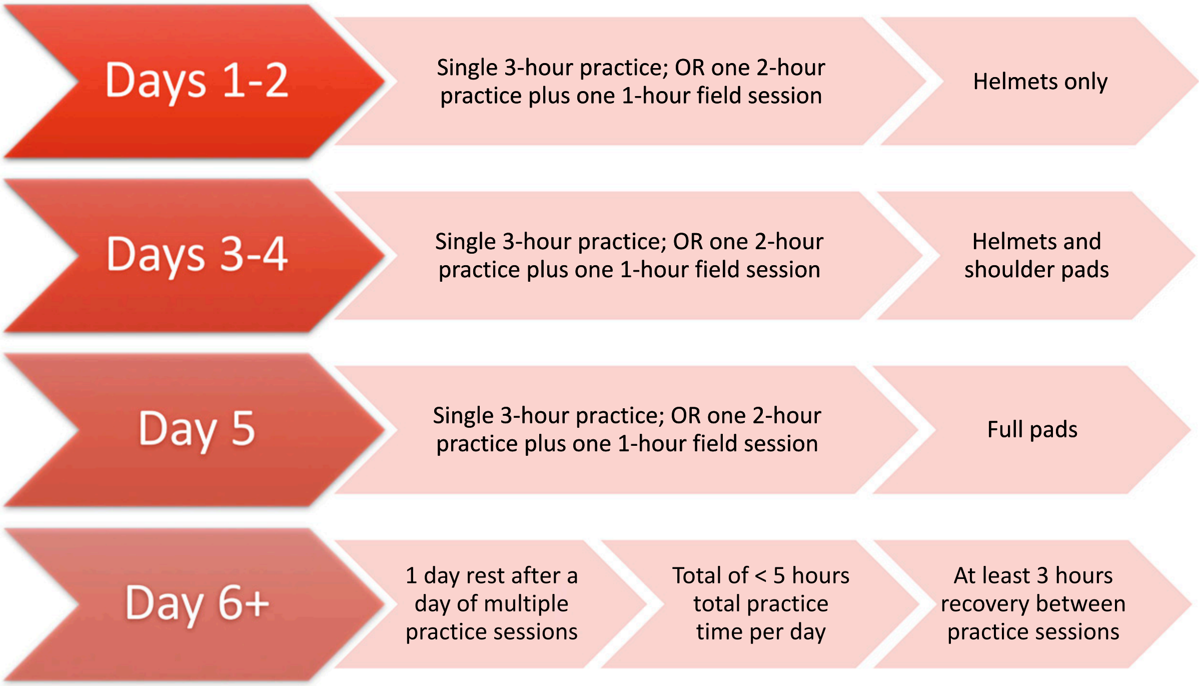
Nonexertional Heat Stroke Prevention

Pediatricians must be prepared to educate families and patients about the dangers of heat exposure. As the weather changes, families should receive basic counseling about appropriate clothing and coverage (bundling) for infants and children with special needs who cannot modify their behavior in response to high environmental temperature or overheating. Special attention should be paid to hydration status during periods of high heat and humidity as infants

TABLE 2. **Complications of Heat Stroke and Recommended Diagnostic Tests**

ORGAN SYSTEM	COMPLICATIONS	EVALUATION
Cardiac	Arrhythmia High-output heart failure and cardiogenic shock	Electrocardiogram Troponin, echocardiogram
Electrolytes and gastrointestinal	Hyponatremia, hypokalemia Lactic acidosis Renal injury or failure Hypocalcemia Liver injury or failure, gut edema	Basic metabolic panel Venous blood gas, lactate Urinalysis, urine output, electrolytes Ionized calcium Liver function tests, coagulation panel
Neurologic	Altered mental status Seizures, cerebral edema	Dextrose stick, urine toxicology Consider head CT or EEG if not improving with cooling
Musculoskeletal	Rhabdomyolysis	Creatine kinase
Pulmonary	Pulmonary edema	Chest radiograph
Hematologic	Anemia Disseminated intravascular coagulation	Complete blood cell count Coagulation panel, D-dimer, fibrinogen

CT=computed tomography, EEG=electroencephalogram.



Days 1-2	Single 3-hour practice; OR one 2-hour practice plus one 1-hour field session		Helmets only
Days 3-4	Single 3-hour practice; OR one 2-hour practice plus one 1-hour field session		Helmets and shoulder pads
Day 5	Single 3-hour practice; OR one 2-hour practice plus one 1-hour field session		Full pads
Day 6+	1 day rest after a day of multiple practice sessions	Total of < 5 hours total practice time per day	At least 3 hours recovery between practice sessions

Figure 2. Acclimatization recommendations. (Adapted with permission from Casa DJ, DeMartini JK, Bergeron MF, et al. National Athletic Trainers' Association position statement: exertional heat illnesses. *J Athl Train.* 2015;50(9):986–1000.) (14)

and children with special needs may have increased insensible losses that will require supplementation of additional fluids (human milk, tube feeds, free water, etc).

When it comes to vehicular-related HRI and classic heat stroke, there are many prevention strategies that can be used. Caregivers should be advised to never leave their child unattended in a vehicle and to keep car doors locked when not in use to prevent entrapment. (21) The organization KidsAndCars.org has launched an educational campaign that encourages caregivers to "Look Before You Lock." (34) Others suggest that the driver place a meaningful object (a purse, briefcase, or shoe) in the rear seat so that they are forced to check the back seat before exiting the vehicle.

Technology may also help prevent vehicular HRI. General Motors has developed a "Rear Seat Reminder" system to alert drivers to check the back seat once the vehicle is turned off. Future innovations may use sensors to detect the presence of an occupied rear seat and alert the driver accordingly. Last, the federal government may play a role in enforcing meaningful change. Lawmakers are considering legislation that will require the National Highway Traffic Safety Administration to set regulations enforcing automakers to equip vehicles with an alert system to remind parents to check the rear seat. (35)

Exertional Heat Stroke Prevention

Regarding exertional heat stroke prevention, various regulatory bodies, such as the American Academy of Pediatrics, the National Collegiate Athletic Association, and the National Athletic Trainer's Association, have established policy statements to guide education, management, and prevention of HRI in athletes, and their recommendations are summarized in the following subsections. (9)(14)(24) It is important for pediatricians, coaches, athletic directors, athletes, and caregivers to be familiar with identifying signs and symptoms of HRI as well as preventing these dangerous conditions. (9)

Screening. Before initiation of athletic activity, all athletes should undergo a preparticipation history and physical examination to identify any health conditions or medications that may predispose them to HRI. Athletes should be counseled about the risks of HRI and effective prevention measures. Caregivers and coaches should recognize that athletes with recent or current febrile or gastrointestinal illnesses should not be permitted to participate.

Acclimatization. As the athletic season begins, teams should follow guidelines for safe acclimatization. Training and conditioning for fall sports (eg, football) typically occur in August, during the warmest days of the year. Athletes should acclimatize to warm weather and increase activity over 1 to 2 weeks. The intensity and duration of physical activity should increase gradually during this period.

Athletic Gear and Garb. Athletes should wear light-colored garments that are lightweight and loose-fitting. Uniforms and practice gear should be made from open-weave or

TABLE 3. **Daily Water Intake Recommendations by Age and Sex**

AGE	SEX	TOTAL DAILY WATER CONSUMPTION, L[a]
0–6 mo	All	0.7
7–12 mo	All	0.8
1–3 y	All	1.3
4–8 y	All	1.7
9–13 y	Girls	2.1
	Boys	2.4
14–18 y	Girls	2.3
	Boys	3.3

[a] *Total water consumption includes all beverage and food sources of water. (37)*

sweat-wicking materials to facilitate evaporative heat loss. (6) Sweat-saturated garments should be removed promptly. (10) The amount of athletic equipment should be worn in incremental steps, as described in Fig 2. (14)

Hydration. Players should be encouraged to adequately hydrate before, during, and after physical exertion. During activity, players should have access to water and salt-containing beverages and should be allowed dedicated time to hydrate. (9) Offering flavored hydration products (such as sports drinks) has been shown to increase consumption and reduce dehydration. (36) Table 3 reviews guidelines for daily fluid intake.

Scheduling. When weather is extremely hot, practices should be scheduled for mornings and evenings, when temperatures are generally cooler. (24) Contingency plans should be in place to reschedule practices or games if heat or humidity is expected to be severe. The Wet Bulb Globe Temperature (WBGT) is an index of heat stress that accounts for temperature, humidity, and radiation. The WBGT may be used as an objective measure to assess whether environmental conditions pose a significant risk of HRI to athletes. There are published guidelines that suggest specific limitations on physical activity based on the WBGT. (8)(10) When the WBGT is not available, the heat index may also be used to guide decisions about activity and event scheduling.

Preparation. Medical equipment and resources for rapid cooling (cold-water tubs, ice towels, rectal thermometers, etc) should be available at athletic events. (9) There should be preestablished guidelines for practice and playing in heat and humidity. An emergency action plan should be in place should any athlete demonstrate signs or symptoms of heat exhaustion or heat stroke. (9)

Summary

- Based on observational studies (Evidence Quality C), the incidence of heat-related illnesses is increasing as the planet has more extreme heat waves; based on expert opinion (Evidence Quality D), clinicians must heighten awareness for caregivers and patients in prevention efforts. (1)(2)(3)(4)
- Based on strong research evidence (Evidence Quality A), heat stroke is differentiated from heat exhaustion by the presence of an elevated core temperature (≥104°F [≥40°C]) and neurologic dysfunction or altered mental status. (2)(11)
- Based on randomized, controlled trials and overwhelmingly consistent evidence from observational studies (Evidence Quality B), first-line management of heat stroke includes measuring a core temperature; assessing the airway, breathing, and circulation; and initiating cooling. Athletes with exertional heat stroke should undergo cold-water immersion when available. (8)(26)(27)(30)
- Based on observational studies (Evidence Quality C), children left in parked cars are vulnerable to heat-related death. Based on expert opinion (Evidence Quality D), parents should be counseled to never leave their child unattended in a vehicle. A useful reminder is to "look before you lock." (20)(21)(23)(34)
- Based on observational studies (Evidence Quality C), coaches and athletic trainers must be familiar with the signs and symptoms of heat stroke and use prevention methods, including appropriate acclimatization time, adequate hydration, and strategic athletic event scheduling. (9)(14)(24)

References for this article are at http://pedsinreview.aappublications.org/content/40/3/97.

PIR Quiz

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1. Individual CME quizzes are available via the blue CME link under the article title in the Table of Contents of any issue.
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1. A 16-year-old male adolescent is attending a crowded rock concert on a summer evening for which he has a standing room–only ticket. He has a syncopal episode lasting for 30 seconds. He was caught by his friend before falling to the ground. The emergency medical service is called, and the patient is moved to the security room. His heart rate is 90 beats/min, respiratory rate is 12 breaths/min, and blood pressure is 110/70 mm Hg. His body temperature is 98.6°F (37°C). His mucous membranes are dry, and he is alert to time and place. Which of the following is the most appropriate treatment measure in this patient?
   - A. Immerse the patient in ice-cold water.
   - B. Place the patient in an air-conditioned room and administer intravenous fluids.
   - C. Place the patient in a supine position and offer oral fluids.
   - D. Place the patient in a supine position and offer fluids and static stretching.
   - E. Spray the patient with lukewarm water and use fans to maximize air circulation.
2. A 17-year-old physically fit female adolescent accepted a dare to run 5 miles on a main highway at noon, where there are no trees or shady areas, near the ocean and then jump into the ocean on a very hot summer day where the outside temperature was 95°F (35°C). Just as she approached the beach she fainted. She was found to be diaphoretic, tachycardic, and hypotensive. Her temperature was 103°F (39.4°C). She appeared to be slightly disoriented to time and place, and she vomited once. Which of the following is the most likely diagnosis in this patient?
   - A. Heat cramps.
   - B. Heat edema.
   - C. Heat exhaustion.
   - D. Heat stroke.
   - E. Heat syncope.
3. A 13-year-old girl with bipolar disorder is brought to the emergency department with altered mental status, a temperature of 105°F (40.6°C), and muscle rigidity. Which of the following pieces of information in the history is most important to aid in making a diagnosis in this patient?
   - A. Family history of fever, muscle rigidity when exposed to inhalational anesthetics.
   - B. History of heat exposure.
   - C. History of travel to the Midwest.
   - D. History of strenuous exercise.
   - E. The patient has been taking risperidone.
4. A 17-year-old boy is delivering newspapers on his bicycle on a hot summer day. He has been found unconscious in a driveway by a neighbor. The neighbor calls 911 and the ambulance arrives. He is delirious when he is aroused and hypotensive, with a temperature of 105°F (40.6°C). Which of the following prognostic indicators best correlates with the severity of the initial injury in this patient?
   - A. Duration of hyperthermia.
   - B. Gastrointestinal hemorrhage.
   - C. Glasgow Coma Scale score of 10.
   - D. Hemoptysis.
   - E. Hypotension.

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5. Ryan, a high school senior, is obtaining clearance from his pediatrician to participate in high school football, which starts practice in August. In providing anticipatory guidance, which of the following prevention measures will most likely have the weakest effect in reducing the risk of exertional heat stroke in this patient?

   A. Access to water and salt-containing beverages.
   B. Acclimate to the warm weather gradually starting with maximum activity during the first few days.
   C. Advise against practicing if he currently has or recently had a gastrointestinal illness.
   D. Loose-fitting clothing.
   E. Uniform made from open-weave material.

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The Sports Preparticipation Evaluation

Shane M. Miller, MD, FAAP,* Andrew R. Peterson, MD, MSPH, FAAP†

*Departments of Orthopaedics and Pediatrics, UT Southwestern, and Texas Scottish Rite Hospital for Children Sports Medicine Center, Dallas, TX
†Departments of Pediatrics and Orthopaedics/Rehabilitation, University of Iowa, Iowa City, IA

Practice Gaps

Lack of familiarity with current recommendations diminishes the confidence to perform a preparticipation physical evaluation (PPE). In a 2014 survey, Madsen et al (1) reported, "Only 37% of physicians reported an awareness of the PPE Monograph." (2) Clinicians should be aware of current guidelines for performing a PPE and identify children who may be at increased risk from sport participation.

Objectives

After completing this article, readers should be able to:

1. Perform a preparticipation history and physical examination and identify children and adolescents who may be at increased risk for morbidity or mortality from sport participation.
2. Recognize that the mandatory preparticipation physical evaluation serves as an opportunity to address medical and psychosocial issues not necessarily associated with sport participation and as an entry point for healthy adolescents into the health-care system.
3. Recognize the cardiac risks associated with sport participation and when additional cardiac evaluation is required.
4. Understand the importance of assessing and documenting neurocognitive function before sport participation.
5. Identify which sports are appropriate for athletes with some common medical conditions.
6. Recognize the effect of a febrile illness on sport participation.

INTRODUCTION

In the United States, sport participation is increasing, with more than 60 million children and adolescents competing in organized sports every year. The number of high school athletes has increased from 7.2 million to 7.9 million during the past 10 years. (3) The physical and psychosocial benefits of sport participation are well-documented, and pediatricians serve a vital role in promoting physical activity. As a pediatrician who is trusted to provide guidance on the health and safety of our children, it is important to be knowledgeable about the current recommendations and controversies regarding the preparticipation physical evaluation (PPE).

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ABBREVIATIONS

AAP	American Academy of Pediatrics
AAS	anabolic-androgenic steroid
AHA	American Heart Association
BP	blood pressure
CDC	Centers for Disease Control and Prevention
DM	diabetes mellitus
ECG	electrocardiography
FDA	Food and Drug Administration
LVH	left ventricular hypertrophy
PES	performance-enhancing substance
PPE	preparticipation physical evaluation
SCAT5	Sports Concussion Assessment Tool, Version 5
SCD	sickle cell disease
SCT	sickle cell trait

The American Academy of Pediatrics (AAP) along with 5 other organizations, including the American Academy of Family Physicians, the American College of Sports Medicine, and the American Medical Society for Sports Medicine, developed the Fourth Edition of the PPE Monograph, (2) which was released in 2010 and describes the standard of care for the PPE. It is a useful and accessible document that offers a standardized approach to the PPE that should be adopted by the pediatric clinician. The Fifth Edition is anticipated to be released soon.

The primary objective of the PPE is to screen for potentially life-threatening conditions or conditions that may put the athlete at risk for injury or illness. Although the PPE has been routinely performed for almost 40 years, there is much discussion as to whether it achieves the intended outcomes. Recently, this debate has centered on cardiac screening and particularly the use of electrocardiography (ECG) to identify potentially life-threatening arrhythmias and structural congenital heart disease. In the United States, ECG has not been a recommended component of a routine PPE due to concerns related to the sensitivity and specificity of the ECG as a screening tool in young athletes. The American Heart Association (AHA) currently recommends a thorough personal history, family history, and physical examination for preparticipation cardiovascular screening of competitive athletes. (4)

However, it is not just ECG screening that has questionable utility. The entire PPE has a remarkably small evidence base to suggest any efficacy for improving the health of young athletes. However, most clinicians still feel that it is an important part of preventive medicine, primarily because the PPE serves as an entry point into the health-care system for otherwise healthy adolescents. For many young athletes, clearance for sports may be the only reason they will have an encounter with a health-care provider. Similar to a well-child examination, this allows the pediatrician to assess the overall health of the young athlete, review the personal and family history, and discuss important psychosocial and medical topics with the patient. In addition, the PPE serves as an opportunity to educate the athlete about topics such as injury prevention, performance-enhancing supplements, concussion, etc. The PPE is also commonly required to fulfill the legal and insurance requirements for participation in athletic activity.

TIMING AND SETTING

Athletes should be encouraged to complete their PPE at least 6 weeks before the first practice. This allows for further investigation or treatment of any issues identified during the evaluation without unnecessarily restricting or delaying sport participation. The beginning of summer or near the end of the previous school year is an ideal time. A comprehensive PPE with a complete personal and family history and thorough physical examination should be performed at least every 2 years, with an annual review of the patient's history and a problem-focused examination as needed. However, because this is often the only interaction an adolescent athlete may have with a health-care provider, it is reasonable to perform a comprehensive evaluation as was done for annual health supervision visits for earlier ages.

The ideal setting is an individual office-based evaluation with the athlete's personal primary physician. Athletes should be encouraged to have a medical home and to have their PPE performed by their primary clinician. This leads to greater continuity of care and allows access to medical records. The athlete's primary care physician is often more familiar with the athlete's previous issues and family history. The primary care physician is also better able to identify changes over time and react appropriately. Many health insurance companies reimburse for only 1 preventive visit per 12 months, so it is reasonable to incorporate the PPE into the annual health supervision visit. Providers may choose to include the components of the PPE as part of the annual health supervision visit for all patients because physical activity should be encouraged regardless of sport participation.

Mass PPE events, such as a group evaluation in a gymnasium or locker room, should be discouraged for several reasons. The close quarters may limit privacy and discourage disclosure of potentially embarrassing concerns for the athlete. These environments are often too noisy to perform an adequate cardiac examination. In addition, medical records are often unavailable or incomplete. A coordinated medical team may administer group evaluations and is an acceptable alternative to the individual office-based examination in certain circumstances. For example, at the collegiate or professional level, the sports medicine team, led by the team physician, may have extensive knowledge of the athlete's background and is well-suited to perform a thorough and adequate PPE. The primary advantage of the group PPE is increased efficiency. Often an entire team or school can complete their PPEs in a short period.

A variation on the mass PPE is the station-based evaluation. Multiple specialists may collaborate and each perform a portion of the evaluation. For example, an orthopedic surgeon may complete the musculoskeletal portion of the examination, a cardiologist may perform a cardiac examination, and a primary care physician may assimilate all of the information to make a determination for clearance to participate.

A physician, specifically the athlete's personal primary physician, is the preferred medical provider to perform the PPE. However, a variety of other health-care professionals may be permitted to complete the evaluation and clear an athlete, so it is important to know your local and state requirements regarding who has the authority to perform a PPE in your area.

HISTORY

Obtaining an accurate and thorough medical history is essential and has been shown to be much more sensitive for detecting abnormalities, such as a history of sickle cell trait (SCT), diabetes mellitus (DM), or seizure disorder, than the physical examination portion of the PPE. The medical history alone detects almost 90% of the medical conditions and 70% of the musculoskeletal conditions identified on the PPE. (5) Parents should be involved and contribute to this element of the PPE because studies have demonstrated poor correlation (<40% agreement) between athlete and parental reports of medical history. (6)

The Fourth PPE Monograph offers a form that is publicly available and encouraged for use among pediatric providers (Appendix A). Some states require a state-specific form that may not address all of the recommended historical components. Because this often serves as the only health examination that a young athlete may receive, additional history should be obtained whenever necessary. The history questions are broken down into several categories, and the importance of these issues are discussed in detail herein.

A history of disqualification from sport participation or restricted participation is a significant finding. Although approximately 10% (3.1%–13.9%) of athletes have a significant finding during the PPE that warrants further investigation or management before clearance, only 1% to 2% of athletes are ultimately disqualified from participation. (7) Therefore, it is reasonable to start by asking the patient whether he or she has ever been restricted or denied participation for any reason in the past.

MEDICAL HISTORY

A broad review of chronic medical conditions allows the provider to gain an understanding of the general health of the athlete and to ensure that any chronic conditions are appropriately managed before clearance for sport participation. For example, poorly controlled DM or asthma may place the athlete at increased risk for morbidity or mortality, regardless of sport participation. It is important to realize that the PPE offers an opportunity for the provider to address general medical concerns for the adolescent patient.

Diabetes

Aerobic exercise and strength training are generally beneficial for patients with DM. However, poor glycemic control or a poor understanding of how insulin and carbohydrate needs might change during exercise can put the diabetic athlete at risk for dangerous hyperglycemia or hypoglycemia. All children and adolescents with DM should be monitored by a clinician with expertise in diabetic management and should be encouraged to discuss the demands of their particular sport with this specialist. Furthermore, the athlete's coaches and on-site medical providers (such as Certified Athletic Trainers) should be competent in delivering emergency diabetic medications, such as glucagon for the treatment of extreme hypoglycemia. Rarely, complications of DM, such as retinopathy, neuropathy, nephropathy, or other microvascular disease, might affect the ability of the athlete to participate safely in sports.

Adequate glycemic control before exercise is imperative, and athletes should be educated on the risk of hypoglycemia during and after exercise, with recommendations for blood glucose monitoring before, during, and after exercise. It is important for the athlete and others to be knowledgeable about the athlete's DM to properly adjust insulin and carbohydrate intake. A DM ID bracelet or shoe tag is recommended to help expedite recognition and treatment of a hypoglycemic episode. Sports such as scuba diving, skydiving, and rock climbing are considered especially high risk for patients with DM due to the consequences of a hypoglycemic episode during these events.

Allergies

A history of a severe allergic reaction or anaphylaxis provides the opportunity to plan for an emergency. Two of the most common causes of anaphylaxis, insect envenomation and food allergies, are commonly encountered in the athletic setting as athletes are often practicing or competing outdoors or may be traveling for various competitions and eating in new environments. Any athlete who reports a previous severe allergic or anaphylactic reaction should be required to have injectable epinephrine on-site for immediate use, and coaches and medical staff should be educated on how to detect and treat potentially life-threatening allergic reactions.

Mononucleosis

There is an increased risk of splenic rupture within the first 21 days of illness in patients with infectious mononucleosis. However, splenic rupture rarely occurs beyond 28 days from the onset of symptoms. Unfortunately, physical examination has proved to have poor sensitivity for splenomegaly and cannot be relied on to determine whether an athlete is at increased risk for splenic rupture. Ultrasonography is also unreliable in detecting splenomegaly due to variation among individuals and lack of defined "normal" spleen size. Because splenomegaly is almost universally present in patients with infectious mononucleosis and often persists for several weeks, physical activity should be restricted completely for 3 to 4 weeks from the onset of symptoms. Symptoms such as fatigue may limit the ability to return to athletic participation for longer periods.

Sickle Cell Trait and Disease

According to the Centers for Disease Control and Prevention (CDC), "sickle cell disease affects approximately 100,000 Americans" and "1 out of every 365 Black or African-American births." (8) Sickle cell trait is the presence of a single sickle cell gene (hemoglobin SA) and affects 1.5% of all US newborns and 7% of black newborns. (9) Acute exertional rhabdomyolysis is associated with SCT and is a leading cause of atraumatic death in athletes, behind only sudden cardiac death and exertional heat stroke. (10) Although athletes with SCT may safely participate in most sports, intense exertional activity performed in hot, humid, or high-altitude environments may lead to exertional sickling. This, in turn, causes vaso-occlusion and ischemia, which leads to rhabdomyolysis. Early recognition of an athlete with sickling collapse may prevent permanent end-organ damage and death. Screening of all athletes for SCT remains controversial but is mandated for National Collegiate Athletic Association athletes. It is important to ask the athlete and his or her family whether there is a family history of sickle cell disease (SCD) or whether the athlete has known SCT. Often, this information can be retrieved from the results of the athlete's newborn screen. Exertional sickling episodes may be prevented by modifying practice and conditioning (eg, avoiding repetitive sprints and/or allowing the athlete to work at his or her own pace with adequate recovery periods), particularly in hot or humid environments, maintaining hydration, and avoiding or acclimatizing to activity at higher altitudes.

The National Athletic Trainers' Association Consensus Statement on SCT (11) recommends the following:

- There is no contraindication to participation in sport for the athlete with SCT.
- Red blood cells can sickle during intense exertion, blocking blood vessels and posing a grave risk for athletes with SCT.
- Screening and simple precautions may prevent deaths and help athletes with SCT thrive in their sport.
- Efforts to document newborn screening results should be made during the PPE.

Although much has been written about screening and the care of the athlete with SCT, SCD in athletes is relatively unexplored. Children and adolescents with SCD (or other blood diseases) should be encouraged to participate in exercise. (12) However, sport participation in this group can be challenging. Sickle cell disease increases the athlete's risk of dehydration, heat injury, exhaustion, painful crises, and joint-related problems. These risks can be mitigated by either limiting exposure or gradually acclimatizing to heat, humidity, and/or high altitude. Similar to all athletes, those with SCD should have unrestricted access to water during practice and competition, and dehydration should be avoided.

Paired Organs

Absence of a paired organ (testicle, kidney, ovary, eye) does not disqualify a patient from athletic participation but may affect clearance for certain sports. Protective equipment may be recommended (such as a protective cup for an unpaired testicle or a flak jacket for a solitary kidney), particularly for high-impact or collision sports. Of note, kidney injury is more likely to occur from a fall from a bicycle than from playing contact sports.

Protective eyewear with American National Standards Institute–approved lenses made of polycarbonate is recommended for sports with a high risk of eye injury (eg, baseball, hockey, fencing, and racquetball). Full goggles with a strap to secure the lenses to the head are preferable because they not only offer prevention of eye injury but may also have prescriptive lenses to provide vision correction. Athletes should not be permitted to play sports in their standard eyeglasses. Contact lenses do not confer any eye protection.

Functionally 1-eyed (absence of 1 eye or best-corrected vision of <20/40 in 1 eye) athletes must wear protective eyewear with American National Standards Institute–approved lenses made of polycarbonate, even in noncontact and low-risk sports. These patients should not be allowed to participate in sports in which the eyes cannot be adequately protected (such as wrestling and full-contact martial arts) because the effects of loss of the good eye can be disastrous.

Acute Illness

Fever increases cardiopulmonary effort and disrupts the body's ability to dissipate heat and maintain thermoregulation, which increases the risk of heat illness. For reasons that are not completely clear, exercising with fever seems to increase the risk of symptomatic myocarditis, and athletes who are acutely febrile should not be permitted to train.

Acute upper respiratory tract infections are common, and athletes may be allowed to participate as long as symptoms remain in the head and neck (eg, pharyngitis, rhinitis, and sinusitis), but symptoms that involve the body, such as chest congestion, productive cough, or myalgias, may indicate a more serious infection and should preclude training and competition.

Supplements

All athletes should be asked about use of alcohol, tobacco, drugs, and performance-enhancing substances (PESs). The PPE offers an opportunity to discuss substance use and abuse with the young athlete and to counsel regarding associated risks. Performance-enhancing substances include dietary supplements as well as legal and illegal drugs, and PESs are commonly used or abused by young athletes to improve athletic performance and/or for aesthetic purposes. Some of the more commonly used PESs are protein, creatine, caffeine, and nonprescription diet pills. Use of PESs increases with age and is generally more prevalent in males (with the exception of diet pills). (13) Thirty-nine percent of 12th-grade males and 30% of eighth-grade males report taking protein supplements at some point, but the use of anabolic-androgenic steroids (AASs) is much lower, with an estimated 3.2% lifetime prevalence of AAS use among high school students. (14)

Concerns regarding PES use among adolescents include the adverse and long-term health effects, which are largely unknown in the pediatric population, as well as risks of contamination because these substances are not regulated by the Food and Drug Administration (FDA). In one study, 25% of over-the-counter supplements tested were contaminated with AASs, and 11% were contaminated with stimulants. (15)

CARDIOVASCULAR

Sudden cardiac death is a rare but devastating event. Young athletes are often perceived as models of fitness and health. When one of these young lives is lost in a sudden and unexpected manner, the tragedy often receives a large amount of publicity and media coverage. Fear of sudden cardiac death can lead parents, athletes, coaches, administrators, and medical providers to seek methods for preventing these events. Unfortunately, most athletes who are at risk for sudden cardiac death are asymptomatic until their fatal event, making it difficult to determine who is at risk.

Routine screening using ECG or echocardiography remains controversial, but most experts agree that a thorough personal and family history is important. In the United States, universal ECG screening is not currently required for young healthy people aged 12 to 25 years. However, targeted screening for certain high-risk populations is gaining acceptance.

The AHA has recommended a 14-element cardiovascular screen using the history and physical examination (Table 1). (4)(16)(17) Certain red flags in the athlete's medical or family history warrant further investigation to detect cardiac abnormalities that may increase risk of sudden cardiac death. In a previous *Pediatrics in Review* article, Peterson and Bernhardt (18) recommended the following: "Known congenital heart disease, cardiac channelopathies (such as long QT or Brugada syndrome), any history of myocarditis, and coronary anomalies such as those caused by Kawasaki disease should be evaluated by a cardiologist before sports participation. A personal history of syncope, near-syncope, chest pain, palpitations, or excessive shortness of breath or fatigue with exertion should prompt a more thorough evaluation, either by the primary clinician or a cardiologist. Postexertional syncope is a common occurrence that is frequently elicited in the PPE history. This benign condition should be differentiated from exercise-associated collapse, which occurs during exertion and is an ominous sign of hemodynamically significant cardiovascular disease or ventricular tachyarrhythmias. All patients who experience syncope should undergo electrocardiography, with further testing on a case-by-case basis."

A family history of early sudden cardiac death (before age 50 years), Marfan syndrome, cardiomyopathy, and arrhythmias (especially long-QT syndrome) should prompt further cardiovascular evaluation. Particular attention should be given to any family history of unexplained or poorly characterized deaths, such as those from drowning, unexplained motor vehicle accidents, sudden infant death syndrome, or seizures. These events may actually represent unrecognized sudden cardiac death. (18)

NERVOUS SYSTEM

There are several neurologic conditions that require further investigation before clearance. The most common are concussion or traumatic brain injury, exertional headaches, seizures, recurrent "burners" or "stingers," and transient quadriparesis.

A concussion is a brain injury caused by a direct or transmitted blow to the head that disrupts normal brain function. It is estimated that 1 to 2 million sport-related concussions occur annually in the United States. (19) Athletes frequently sustain more than 1 concussion over their lifetime. Contact or collision sports (Table 2) (20) have an

TABLE 1. **The American Heart Association 14-Element Cardiovascular Screening Checklist for Congenital and Genetic Heart Disease**

MEDICAL HISTORY[a]
Personal history
1. Chest pain/discomfort/tightness/pressure related to exertion
2. Unexplained syncope/near-syncope[b]
3. Excessive and unexplained dyspnea/fatigue or palpitations associated with exercise
4. Previous recognition of a heart murmur
5. Elevated systemic blood pressure
6. Previous restriction from participation in sports
7. Previous testing for the heart, ordered by a physician
Family history
8. Premature death (sudden and unexpected or otherwise) before 50 y of age attributable to heart disease in ≥1 relative
9. Disability from heart disease in a close relative <50 y of age
10. Hypertrophic or dilated cardiomyopathy, long-QT syndrome, or other ion channelopathies, Marfan syndrome, or clinically significant arrhythmias; specific knowledge of genetic cardiac conditions in family members
Physical examination
11. Heart murmur[c]
12. Femoral pulses to exclude aortic coarctation
13. Physical stigmata of Marfan syndrome
14. Brachial artery blood pressure (sitting position)[d]

[a] *Parental verification is recommended for high school and middle school athletes.*

[b] *Judged not to be of neurocardiogenic (vasovagal) origin; of particular concern when occurring during or after physical exertion.*

[c] *Refers to heart murmurs judged likely to be organic and unlikely to be innocent; auscultation should be performed with the patient in both the supine and standing positions (or with Valsalva maneuver), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction.*

[d] *Preferably taken in both arms.*

Reprinted with permission from Maron BJ, Friedman RA, Kligfield P, et al. Assessment of the 12-lead electrocardiogram as a screening test for detection of cardiovascular disease in healthy general populations of young people (12-25 years of age): a scientific statement from the American Heart Association and the American College of Cardiology. J Am Coll Cardiol. *2014; 64(14), 1479-1514. Copyright 2014, with permission from Elsevier.*

increased risk of concussion compared with limited contact or noncontact sports.

During the PPE it is important to obtain a thorough concussion history, including number, date, symptoms, severity, and recovery from previous injuries. It is imperative that an athlete has fully recovered from the most recent concussion before returning to sport participation to reduce the risk of recurrent injury, second impact syndrome, or permanent neurologic sequelae. An athlete must be symptom-free, including during schoolwork, and must complete a graduated return to play progression before being fully cleared to return to sport. Several factors may prompt consideration of disqualification from contact sports, including increasing frequency or severity of injury, prolonged or incomplete recovery, or multiple concussions.

Baseline neurocognitive testing has become increasingly popular, although concerns regarding poor sensitivity, specificity, test-retest reliability, and intentional underperformance (sandbagging) have brought the utility of these tests into question. There are paper-and-pencil, verbal, and computerized versions of neurocognitive testing. The Sports Concussion Assessment Tool version 5 (SCAT5) (21) and the pediatric version (Child SCAT5) are brief neuropsychological test batteries that may be used for both baseline and postinjury assessments. Assessing and documenting neurocognitive function before sport participation allows for comparison with postinjury test results to ensure that the athlete has returned to their preinjury level of function before clearance to return to play. However, it should be made clear that neurocognitive testing should not be the only tool used to diagnose a concussion. Currently, there are no reliable diagnostic tests for sport-related concussion, and it remains a clinical diagnosis.

Headache with exertion is a common complaint and typically benign. Exercise-induced migraine headache can be differentiated from more common benign exertional headaches based on symptoms. Migraine headaches are pulsatile in nature and typically feature a prodromal aura, light and sound sensitivity, and/or nausea. Primary exercise headaches are steady or constant in nature and typically do not have additional coincident symptoms. Both types of headaches can be treated with exercise modification and/or over-the-counter analgesics. Migraine headache may also be treated with abortive medications, such as serotonin receptor agonists (triptans). Neither migraine headaches nor primary exercise headaches are a contraindication to sport participation. Rarely, more malignant causes of headache, such as increased intracranial pressure, intracranial mass, or unresolved intracranial hemorrhage, may present as exertional headaches. Red flags such as papilledema, night headaches, headaches on awakening, neurologic deficits, or other neurocognitive decline

TABLE 2. **Classification of Sports by Contact Type**

CONTACT OR COLLISION	LIMITED CONTACT	NONCONTACT
Basketball	Baseball	Archery
Boxing[a]	Bicycling	Badminton
Diving	Canoeing or kayaking (white water)	Bodybuilding
Field hockey	Cheerleading	Bowling
Football, tackle	Fencing	Canoeing or kayaking (flat water)
Ice hockey[b]	Field events	Crew or rowing
Lacrosse	Floor hockey	Curling
Martial arts	Football, flag	Dancing (ballet, modern, jazz)[c]
Rodeo	Gymnastics	Field events (discus, javelin, shot put)
Rugby	Handball	Golf
Ski jumping	High jump	Orienteering[d]
Soccer	Horseback riding	Power lifting
Team handball	Pole vault	Race walking
Water polo	Racquetball	Riflery
Wrestling	Skateboarding	Rope jumping
	Skating, ice, in-line, roller	Running
	Skiing (cross-country, downhill, water)	Sailing
	Snowboarding[e]	Scuba diving
	Softball	Swimming
	Squash	Table tennis
	Ultimate frisbee	Tennis
	Volleyball	Track
	Windsurfing or surfing	Weight lifting

[a] *Participation not recommended by the American Academy of Pediatrics.*

[b] *The American Academy of Pediatrics recommends limiting the amount of body checking allowed for hockey players 15 years and younger to reduce injuries. (1)*

[c] *Dancing has been further classified into ballet, modern, and jazz since the previous statement was published. (2)*

[d] *A race (contest) in which competitors use a map and compass to find their way through unfamiliar territory.*

[e] *Snowboarding has been added since the previous statement was published. (2)*

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should prompt the clinician to obtain neuroimaging studies.

Seizure disorders (epilepsy) typically improve with exercise, and most athletes with seizures should not be excluded from sport participation. However, there are exceptions when having a seizure could endanger the health or safety of the athlete or those around him or her. For example, athletes with epilepsy should not participate in skydiving, scuba diving, or shooting sports such as riflery or archery. Swimming and diving are generally allowable as long as the athlete is constantly supervised during practice and competition.

Stingers or burners are injuries to the brachial plexus and/or cervical nerve roots. If symptoms are brief in duration and the athlete recovers full strength and sensation between injuries, these injuries are generally benign. An athlete should not be returned to play with a symptomatic stinger, and symptoms that last longer than 48 hours generally require additional evaluation for cervical spine injury. Athletes with frequent recurrent stingers should also be further evaluated to rule out cervical stenosis or other cervical spine abnormalities that might put them at risk for more severe neurologic injury. If an athlete presents with bilateral stingers, he or she should be disqualified from contact sport participation until his or her cervical spine has been fully evaluated.

Transient quadriparesis, also known as cervical spine neuropraxia, is a common and dramatic event that occurs when the cervical spine is concussed. The athlete typically loses most or all motor control of all 4 extremities. It is generally a benign condition as long as the athlete recovers full neurologic function within a few hours of the event. However, these events are so dramatic that it is reasonable to obtain brain and cervical spine neuroimaging to ensure that the athlete has not sustained a more severe injury and that the athlete does not have an underlying cervical spine stenosis or other structural abnormality. Management of the athlete who is symptomatic for more than 24 hours is controversial and should prompt most providers to obtain expert consultation.

MUSCULOSKELETAL

The musculoskeletal history has demonstrated excellent sensitivity for detecting injuries or conditions that may affect sport participation. (22) Inquiring about any injury or complaint that caused the athlete to miss time from their sport or required surgery, casting, bracing, taping, use of crutches, imaging, evaluation by a medical professional, or rehabilitation will identify most musculoskeletal problems that require further evaluation or treatment.

PULMONARY

Exercise-induced bronchospasm affects 12% to 15% of athletes and is more common in athletes with allergic rhinitis and/or allergic asthma. (23) Well-controlled asthma is not a contraindication to sport participation. Most athletes with EIB will benefit from use of a bronchodilator approximately 20 to 30 minutes before exercise. Any athlete with asthma should have an asthma action plan, a metered-dose inhaler on-site for immediate use, and consideration for multiple inhalers (one at home, one at school).

FEMALE ATHLETES

A menstrual history, including menarchal status, age at menarche, and how many periods have occurred in the past 12 months, will help identify athletes at increased risk for female athlete triad (24) (Table 3). The triad is defined as a medical condition often observed in physically active girls and women and involves 3 components (25): low-energy availability with or without disordered eating, menstrual dysfunction, and low bone mineral density.

It is estimated that 16% to 54% of high school female athletes will have 1 component, and that 1.2% will have all 3 components of the triad. (26) Athletes involved in activities that tend to be associated with low body weight (eg, running and ballet dancing) or sports in which scoring is subjective (eg, figure skating and gymnastics) have a higher risk of the triad. A history of stress fracture or restricted dietary intake (eg, a vegan diet) may also indicate an athlete at risk for the triad.

Anemia is associated with heavy or frequent menstrual cycles and nutritional energy deficit. Iron is best obtained through the diet, particularly with the consumption of red meats containing high levels of heme iron. Athletes that follow a strict vegan diet may be at increased risk for iron deficiency due to poor iron bioavailability as well as low iron intake.

PSYCHOLOGICAL

Eating disorders, depression, anxiety, and other psychological or psychiatric conditions commonly affect athletes. Although no psychological condition is an absolute contraindication to sport participation, the provider should consider how these conditions might affect sport participation. Screening for disordered eating should be part of every PPE, and occasionally sport participation will need to be deferred, modified, or closely monitored if the athlete has a life-threatening or poorly controlled eating disorder. Athletes with a history of disordered eating should be monitored by their team's medical personnel (team physician and/or athletic trainer) to ensure continued safe participation during the season. Depression and anxiety can be worsened by the psychological demands of sport participation. However, sport participation is beneficial for most athletes with psychological conditions.

IMMUNIZATION

The PPE is an opportunity to assess immunization status and perform routine or catch-up immunizations. Some athletes travel extensively for their sport, and it may be important to address the need for immunizations or other prophylactic treatment if the athlete intends to travel to areas where preventable illnesses are common. In addition, some athletes commonly share close quarters or have frequent

TABLE 3. The Female Athlete Triad Coalition's Recommended Screening Questions for the Female Athlete Triad

QUESTION	INCLUDED ON THE 4TH-EDITION PPE FORM
1. Do you worry about your weight or body composition?	Yes
2. Do you limit or carefully control the foods that you eat?	Yes
3. Do you try to lose weight to meet weight or image/appearance requirements in your sport?	Yes
4. Does your weight affect the way you feel about yourself?	No
5. Do you worry that you have lost control over how much you eat?	No
6. Do you make yourself vomit or use diuretics or laxatives after you eat?	No
7. Do you currently or have you ever suffered from an eating disorder?	Yes
8. Do you ever eat in secret?	
9. What age was your first menstrual period?	Yes
10. Do you have monthly menstrual cycles?	Yes
11. How many menstrual cycles have you had in the last year?	Yes
12. Have you ever had a stress fracture?	Yes

PPE=preparticipation physical evaluation.

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contact with other athletes. For these athletes, it is important to consider immunization for influenza, hepatitis, meningitis, and human papilloma virus.

PHYSICAL EXAMINATION

Vital Signs

Height, weight, and BMI offer data regarding underweight (<5th percentile), overweight (85th–94th percentile), and obesity (≥95th percentile) or possible growth disturbance. However, BMI has substantial limitations as a screening tool in athletes because some athletes with increased lean muscle mass may have a high BMI. Obesity is not a contraindication to sport participation, although it is important to identify athletes who may have complications of their obesity (eg, hypertension, DM, slipped capital femoral epiphysis, etc). Obese patients should be encouraged to exercise safely and may benefit from dietary counseling. Obese athletes commonly gravitate toward sports where size and strength are an advantage (eg, football lineman). However, low-impact aerobic exercise is likely to be more beneficial to the obese athlete who is attempting to lose weight and improve cardiovascular fitness.

Athletes who are extremely thin or underweight may require further evaluation, particularly female athletes who may be at increased risk for the female athlete triad. Underweight is not a contraindication to sport participation, but it does increase risk of injury, especially bony stress injury.

Blood pressure (BP) should be measured after the athlete has been resting for 5 minutes with the arm at heart level using an appropriately sized cuff. Some athletes have very large or very small arms, and using the wrong-sized cuff can make a substantial difference in their BP measurements. Hypertension is the most commonly encountered cardiovascular disease in the athletic population, with 6.4% of athletes presenting for routine PPE found to have an elevated BP. (27) According to The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, (28) "Hypertension is defined as average systolic BP and/or diastolic BP that is ≥95th percentile for gender, age, and height on ≥3 occasions." Although a diagnosis of hypertension should not be made based on an isolated BP reading, the PPE is often the only time a young athlete has their BP taken and is an important step in identifying individuals with hypertension.

The AAP Policy Statement on Athletic Participation by Children and Adolescents Who Have Systemic Hypertension includes the following recommendations (29):

- The presence of prehypertension should not limit a person's eligibility for competitive athletics. Lifestyle modifications, including weight management, daily physical activity, and a well-balanced diet, should be discussed and encouraged. Patients with prehypertension should have their BP measured every 6 months.
- Stage 1 hypertension in the absence of end-organ damage, including left ventricular hypertrophy (LVH) or concomitant heart disease, should not limit a person's eligibility for competitive athletics. These athletes should have their BP rechecked in 1 to 2 weeks to confirm the hypertension or sooner if they are symptomatic. Appropriate referrals to qualified pediatric medical subspecialists need to be made if patients are symptomatic, have LVH or concomitant heart disease, or have persistently elevated BP on 2 additional occasions. Lifestyle modifications should be discussed and encouraged.
- Youth with stage 2 hypertension in the absence of end-organ damage, including LVH or concomitant heart disease, should be restricted from high-static sports that are associated with acute elevation in diastolic pressures (eg, weightlifting, gymnastics) (29) until their BP is in the normal range after lifestyle modification and/or drug therapy. These athletes should be promptly referred and evaluated by a qualified pediatric medical subspecialist within 1 week if they are asymptomatic or immediately if they are symptomatic. Lifestyle modifications should be discussed and encouraged.
- Medication, caffeine, drug, tobacco, and stimulant use should be reviewed with any athlete with hypertension because of the effects that these substances may have on BP.

General

Patients should be screened for stigmata of Marfan syndrome (scoliosis or kyphosis, pectus deformity, increased arm span/height ratio, facial features, thumb sign, wrist sign, myopia, etc). The Marfan Foundation provides an online tool using the revised Ghent criteria to help clinicians diagnose Marfan syndrome.

Head, Eyes, Ears, Nose, and Throat

Visual acuity testing should be performed using a standard Snellen eye chart. Vision should be 20/40 or better in each eye, with or without correction. As previously mentioned, an athlete with best-corrected vision worse than 20/40 in 1 eye is considered to be functionally 1-eyed, and protective eyewear is mandatory in any sport participation. A difference of 2 lines or greater between eyes warrants further evaluation because this may be a sign of amblyopia. Assessment of pupillary size and shape at baseline is helpful, particularly if anisocoria is present as this may be an alarming finding after a concussion that may actually be normal in that patient.

Musculoskeletal

Asymptomatic athletes without a previous injury should undergo a screening musculoskeletal examination (Fig). The musculoskeletal screening examination has limited sensitivity but is sufficient considering the high sensitivity of a musculoskeletal history. This screening examination takes less than 2 minutes to complete.

Any history of injury or symptoms identified on the history portion of the PPE warrant a more detailed examination of that particular body part or joint, and referral for further evaluation or treatment when necessary. Injuries that have not been fully rehabilitated place the athlete at risk for subsequent injury. An athlete must demonstrate pain-free full range of motion, symmetric strength, and stability before clearance to return to participation. Consideration of a protective or supportive device (eg, ankle brace with history of ankle sprain) may allow the athlete to perform at a high level without symptoms or recurrence of injury but should not replace a proper rehabilitation program if deficits are identified on the PPE.

Clinicians may consider adding a joint-specific examination for sports with injury patterns that place specific areas at higher risk. For example, evaluation of the shoulder and elbow in a throwing athlete (eg, baseball, softball) or the knees in a soccer player might identify additional problems but are not required as part of the routine PPE.

Cardiovascular

Cardiac auscultation should be performed in a quiet area to facilitate identification of abnormal heart sounds. The examination is performed in both the supine and standing positions (or with and without Valsalva maneuver) to assess for changes in murmurs of dynamic left ventricular outflow tract obstruction (such as hypertrophic cardiomyopathy). The murmur of hypertrophic cardiomyopathy is typically harsh, early systolic, and heard best at the right upper sternal border. It increases in intensity with activities that decrease cardiac preload, such as standing or Valsalva. Benign cardiac flow

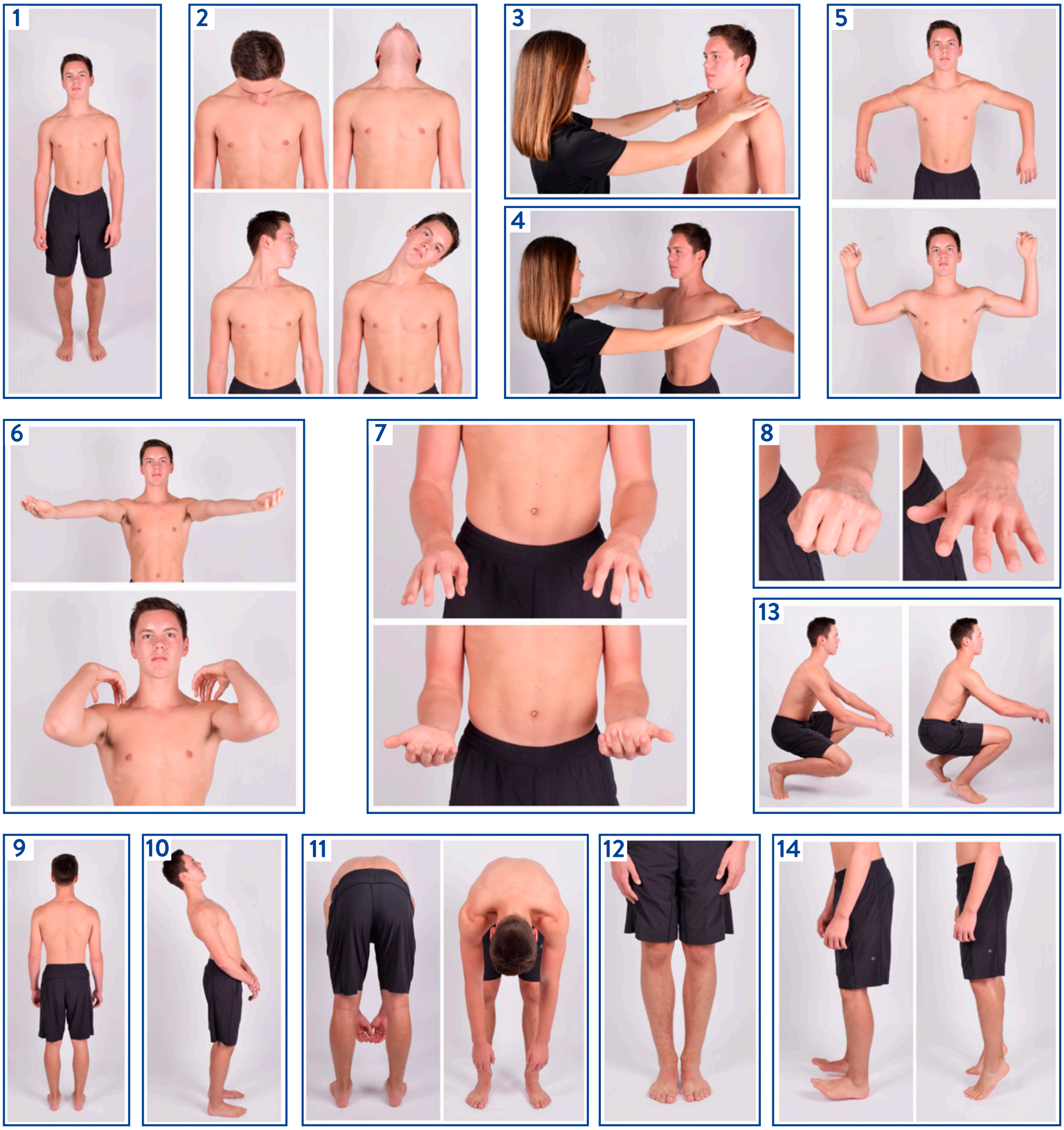

Figure. Musculoskeletal screening examination. The general musculoskeletal screening examination consists of the following: 1) inspection, athlete standing, facing toward examiner (symmetry of trunk, upper extremities); 2) forward flexion, extension, rotation, lateral flexion of neck (range of motion, cervical spine); 3) resisted shoulder shrug (strength, trapezius); 4) resisted shoulder abduction (strength, deltoid); 5) internal and external rotation of shoulder (range of motion, glenohumeral joint); 6) extension and flexion of elbow (range of motion, elbow and wrist); 7) pronation and supination of the elbow (range of motion, elbow and wrist); 8) clench fist, then spread fingers (range of motion, hand and fingers); 9) inspection, athlete facing away from examiner (symmetry of trunk, upper extremities); 10) back extension, knees straight (spondylolysis/ spondylolisthesis); 11) back flexion with knees straight, facing toward and away from the examiner (range of motion, thoracic, and lumbosacral spine; spine curvature; hamstring flexibility); 12) inspection of the lower extremities, contraction of quadriceps muscles (alignment, symmetry); 13) "duck walk" 4 steps (motion of hip, knee, and ankle; strength; balance); 14) standing on toes, then on heels (symmetry, calf; strength; balance).

murmurs are common in athletes but typically decrease in intensity with standing or Valsalva.

Palpation of femoral pulses and comparison with radial artery pulses is important to exclude aortic coarctation. A patient with coarctation will typically have diminished intensity of arterial pulse at the femoral artery compared with the radial artery. Rarely, a delay in pulse transmission can be felt in the femoral arteries. This finding has high specificity for aortic coarctation.

Genitourinary

If performed, a chaperone should be present for any genitourinary examination. Males should be assessed for the presence of 2 descended testicles. The PPE offers an opportunity to educate adolescent males regarding testicular self-examination as a screening tool for early identification of testicular cancer. An undescended testicle carries an increased risk of testicular cancer and warrants referral to urology. Evaluation for inguinal hernias is not required unless there are findings on the history portion that indicate doing so.

A genitourinary examination is not part of the routine PPE in female adolescents unless there is a concerning historical finding or when the PPE also serves as the annual routine health maintenance examination for the female athlete, in which case guidelines for pelvic examination should be followed.

Clearance

Determination of clearance for participation depends on historical and examination findings of the PPE, as well as the activity in which the athlete desires to participate. Most athletes are able to be fully cleared for all sports without restrictions at the time of the PPE. Some athletes will require further evaluation (such as a referral to cardiology for evaluation of a concerning murmur) or treatment (such as a course of rehabilitation to treat an ankle sprain) before full clearance. Additional conditions that may affect sport participation are discussed more fully in the AAP Statement on Medical Conditions Affecting Sport Participation (Appendix B). (20)

Very few athletes (approximately 1%) will not be cleared for sport participation, but disqualification from one sport does not necessarily imply ineligibility for all sports. Any time a patient is restricted from participation, an alternative activity should be recommended. For example, if a patient is restricted from contact sports due to a history of multiple concussions, he or she may still be able to participate in a noncontact sport, such as running track, dance, or tennis.

CONCLUSIONS

Pediatricians should generally feel comfortable managing injury and illness prevention and detecting potentially dangerous medical conditions in athletes and nonathletes alike. The PPE provides some unique challenges and opportunities in a population of children and adolescents who may otherwise rarely seek medical care. These otherwise healthy patients may have no other interaction with a medical professional, so the PPE should be taken seriously by parents, athletes, and medical providers and not treated as just an administrative barrier to sport participation. The PPE Monograph published by the AAP is an excellent resource and offers evidence-based guidelines for pediatricians and other health-care providers.

Summary

- Based primarily on consensus, the preparticipation physical evaluation should be performed by the primary care physician in the patient's medical home.
- Based on some research (4) as well as consensus, cardiovascular screening should include a thorough personal and family history. Routine electrocardiographic screening remains controversial at this time.
- Based on strong research as well as consensus, (30) 60 minutes of daily physical activity is recommended for all children and adolescents and should be encouraged by pediatricians routinely during annual health examinations.

References for this article are at http://pedsinreview.aappublications.org/content/40/3/108.

PIR Quiz

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1. You are seeing a 12-year-old African American boy for a yearly physical and sports preparticipation clearance. You notice that he has sickle cell trait as listed on his problem list diagnosed by newborn screen. The rest of his history and physical examination findings are normal. Which of the following is the most appropriate sport participation clearance recommendation for this patient?
   - A. Clear him and recommend adequate breaks, hydration, conditioning, and avoidance of/acclimatization to high altitudes.
   - B. Clear him for all sports with no special recommendations because he can be treated the same as a healthy 12-year-old.
   - C. Clear him for only low-intensity sports with no special recommendations.
   - D. Exclude him from sport participation to prevent sickling, dehydration, and rhabdomyolysis.
   - E. Limit his exercise to early morning or late in the day when the temperature is cooler to avoid overheating.
2. A 16-year-old female teenager, known to your practice, presents to the clinic for a sports physical. You saw her last month as a follow-up to an emergency department (ED) visit for fainting episodes. She has had multiple fainting episodes during the past 6 months without any known explanation. The episodes are not related to exertion or physical activity. Review of her ED records shows that she had a normal electrocardiogram (EKG), laboratory studies, and brain computed tomographic scan. A referral to cardiology was made by the ED and is pending at this point. Her appointment is 3 months away. The patient says "nothing is wrong" with her and is keen to start soccer in the fall. Her family is, however, worried. Which of the following is the next best step in management?
   - A. Do not clear her for sports until she is cleared by cardiology, and assist the family in expediting the cardiology evaluation.
   - B. Clear her for sports today and cancel the cardiology referral since her studies in the ED were normal.
   - C. Clear her for soccer practice today but not for competition until her cardiology evaluation is completed.
   - D. Clear her for sports today and recommend that she keeps the cardiology appointment in 3 months.
   - E. Clear her for sports today and recommend that she keeps the cardiology appointment in 3 months only if she had recurrence of her symptoms.
3. A 14-year-old boy comes to your office for his yearly physical and wants to return to play soccer in the fall. He has had 2 episodes of concussion in the previous season and has returned to baseline. He was referred to a sports medicine specialist the last time you saw him. You note that the sports medicine specialist ordered neurocognitive testing, which has not been done yet. Which of the following is the best recommendation to give the family today regarding neurocognitive testing in this patient?
   - A. Can be done at any time during the soccer season and will not hold his sports clearance today.
   - B. Is not a sensitive test and, therefore, is not indicated at this time or in the future.
   - C. It is not needed at this time because the patient has fully recovered and is asymptomatic.
   - D. Should be conducted now as a baseline before the next season.
   - E. Should be conducted only if he has another concussion episode in the future.

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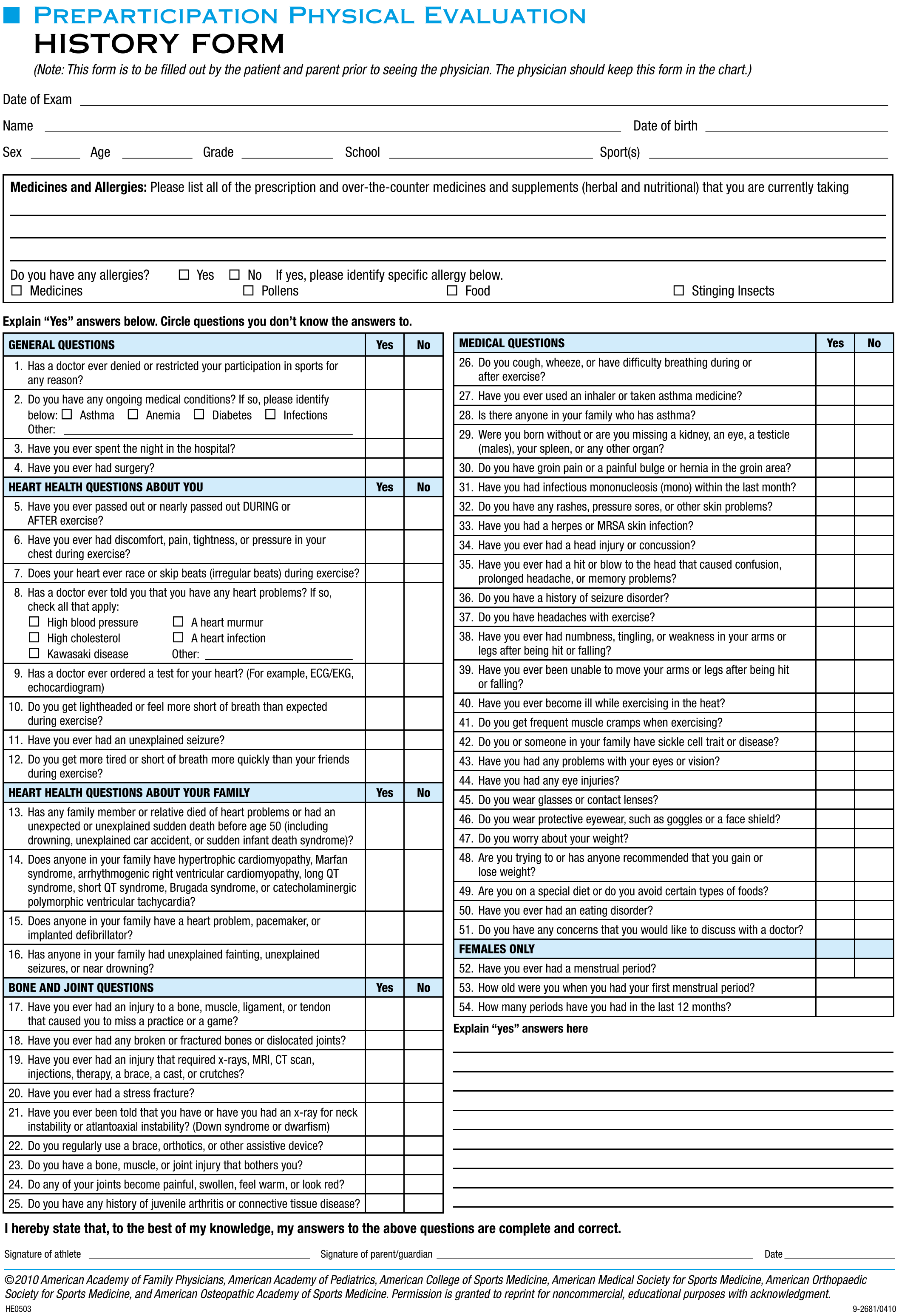
4. A 13-year-old female gymnast is brought to your office for her yearly physical examination and clearance for sports. The mother reports that the patient does not eat much, watches her calories very closely, and obsesses over her weight. Since the last time you saw her, she appears skinny and is less than the 5th percentile for weight. Menarche occurred at 11 years of age. Which of the following additional historical findings is most likely to suggest an increased risk of the female athlete triad in this patient?
    - A. Chronic throbbing headaches associated with exercise.
    - B. High energy level as evidenced by overexercising.
    - C. Hypertension triggered by exercise.
    - D. Maintaining a constant body weight across 12 months.
    - E. Menstrual dysfunction in the past 12 months, such as irregular menses or amenorrhea.
5. A 13-year-old boy is brought to the clinic for his yearly physical examination. His family history is negative for early cardiac deaths in family members. On physical examination you note a harsh, early systolic murmur best heard over the right upper sternal border that increases in intensity on standing. Pulses are normal and equal in all 4 extremities. Which of the following is the next best step in management in this patient?
    - A. Clear him for all sports and order an EKG to be performed in the future at the family's convenience.
    - B. Clear him for all sports and reassure the family that this is a benign heart murmur.
    - C. Clear him for low-intensity sports, no further evaluation is indicated.
    - D. No clearance for sports and follow up on the murmur in 1 year.
    - E. No clearance for sports. Reevaluate after an EKG, echocardiogram, and cardiology clearance are completed.



PREPARTICIPATION PHYSICAL EVALUATION

HISTORY FORM

(Note: This form is to be filled out by the patient and parent prior to seeing the physician. The physician should keep this form in the chart.)

Date of Exam ______________________________

Name ______________________________ Date of birth ______________

Sex ______ Age ______ Grade ______ School ______________ Sport(s) ______________

Medicines and Allergies: Please list all of the prescription and over-the-counter medicines and supplements (herbal and nutritional) that you are currently taking

____

____

____

Do you have any allergies? ☐ Yes ☐ No If yes, please identify specific allergy below.
☐ Medicines ☐ Pollens ☐ Food ☐ Stinging Insects

Explain "Yes" answers below. Circle questions you don't know the answers to.

GENERAL QUESTIONS	Yes	No
1. Has a doctor ever denied or restricted your participation in sports for any reason?		
2. Do you have any ongoing medical conditions? If so, please identify below: ☐ Asthma ☐ Anemia ☐ Diabetes ☐ Infections Other: ______________		
3. Have you ever spent the night in the hospital?		
4. Have you ever had surgery?		
HEART HEALTH QUESTIONS ABOUT YOU	**Yes**	**No**
5. Have you ever passed out or nearly passed out DURING or AFTER exercise?		
6. Have you ever had discomfort, pain, tightness, or pressure in your chest during exercise?		
7. Does your heart ever race or skip beats (irregular beats) during exercise?		
8. Has a doctor ever told you that you have any heart problems? If so, check all that apply: ☐ High blood pressure ☐ A heart murmur ☐ High cholesterol ☐ A heart infection ☐ Kawasaki disease Other: ______________		
9. Has a doctor ever ordered a test for your heart? (For example, ECG/EKG, echocardiogram)		
10. Do you get lightheaded or feel more short of breath than expected during exercise?		
11. Have you ever had an unexplained seizure?		
12. Do you get more tired or short of breath more quickly than your friends during exercise?		
HEART HEALTH QUESTIONS ABOUT YOUR FAMILY	**Yes**	**No**
13. Has any family member or relative died of heart problems or had an unexpected or unexplained sudden death before age 50 (including drowning, unexplained car accident, or sudden infant death syndrome)?		
14. Does anyone in your family have hypertrophic cardiomyopathy, Marfan syndrome, arrhythmogenic right ventricular cardiomyopathy, long QT syndrome, short QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia?		
15. Does anyone in your family have a heart problem, pacemaker, or implanted defibrillator?		
16. Has anyone in your family had unexplained fainting, unexplained seizures, or near drowning?		
BONE AND JOINT QUESTIONS	**Yes**	**No**
17. Have you ever had an injury to a bone, muscle, ligament, or tendon that caused you to miss a practice or a game?		
18. Have you ever had any broken or fractured bones or dislocated joints?		
19. Have you ever had an injury that required x-rays, MRI, CT scan, injections, therapy, a brace, a cast, or crutches?		
20. Have you ever had a stress fracture?		
21. Have you ever been told that you have or have you had an x-ray for neck instability or atlantoaxial instability? (Down syndrome or dwarfism)		
22. Do you regularly use a brace, orthotics, or other assistive device?		
23. Do you have a bone, muscle, or joint injury that bothers you?		
24. Do any of your joints become painful, swollen, feel warm, or look red?		
25. Do you have any history of juvenile arthritis or connective tissue disease?		

MEDICAL QUESTIONS	Yes	No
26. Do you cough, wheeze, or have difficulty breathing during or after exercise?		
27. Have you ever used an inhaler or taken asthma medicine?		
28. Is there anyone in your family who has asthma?		
29. Were you born without or are you missing a kidney, an eye, a testicle (males), your spleen, or any other organ?		
30. Do you have groin pain or a painful bulge or hernia in the groin area?		
31. Have you had infectious mononucleosis (mono) within the last month?		
32. Do you have any rashes, pressure sores, or other skin problems?		
33. Have you had a herpes or MRSA skin infection?		
34. Have you ever had a head injury or concussion?		
35. Have you ever had a hit or blow to the head that caused confusion, prolonged headache, or memory problems?		
36. Do you have a history of seizure disorder?		
37. Do you have headaches with exercise?		
38. Have you ever had numbness, tingling, or weakness in your arms or legs after being hit or falling?		
39. Have you ever been unable to move your arms or legs after being hit or falling?		
40. Have you ever become ill while exercising in the heat?		
41. Do you get frequent muscle cramps when exercising?		
42. Do you or someone in your family have sickle cell trait or disease?		
43. Have you had any problems with your eyes or vision?		
44. Have you had any eye injuries?		
45. Do you wear glasses or contact lenses?		
46. Do you wear protective eyewear, such as goggles or a face shield?		
47. Do you worry about your weight?		
48. Are you trying to or has anyone recommended that you gain or lose weight?		
49. Are you on a special diet or do you avoid certain types of foods?		
50. Have you ever had an eating disorder?		
51. Do you have any concerns that you would like to discuss with a doctor?		
FEMALES ONLY		
52. Have you ever had a menstrual period?		
53. How old were you when you had your first menstrual period?		
54. How many periods have you had in the last 12 months?		

Explain "yes" answers here

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I hereby state that, to the best of my knowledge, my answers to the above questions are complete and correct.

Signature of athlete ______________ Signature of parent/guardian ______________ Date ______________

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HE0503 9-2681/0410

Appendix A. Preparticipation Physical Evaluation Physical Examination Form. (Reprinted with permission from Bernhardt DT, Roberts WO; American Academy of Family Physicians, American Academy of Pediatrics. *PPE: Preparticipation Physical Evaluation*. 4th ed. Elk Grove Village: American Academy of Pediatrics; 2010.

■ PREPARTICIPATION PHYSICAL EVALUATION

THE ATHLETE WITH SPECIAL NEEDS: SUPPLEMENTAL HISTORY FORM

Date of Exam ______________________________

Name ______________________________ Date of birth ______________

Sex ______ Age ______ Grade ______ School ______________ Sport(s) ______________

1. Type of disability		
2. Date of disability		
3. Classification (if available)		
4. Cause of disability (birth, disease, accident/trauma, other)		
5. List the sports you are interested in playing		
	Yes	**No**
6. Do you regularly use a brace, assistive device, or prosthetic?		
7. Do you use any special brace or assistive device for sports?		
8. Do you have any rashes, pressure sores, or any other skin problems?		
9. Do you have a hearing loss? Do you use a hearing aid?		
10. Do you have a visual impairment?		
11. Do you use any special devices for bowel or bladder function?		
12. Do you have burning or discomfort when urinating?		
13. Have you had autonomic dysreflexia?		
14. Have you ever been diagnosed with a heat-related (hyperthermia) or cold-related (hypothermia) illness?		
15. Do you have muscle spasticity?		
16. Do you have frequent seizures that cannot be controlled by medication?		

Explain "yes" answers here

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Please indicate if you have ever had any of the following.

	Yes	No
Atlantoaxial instability		
X-ray evaluation for atlantoaxial instability		
Dislocated joints (more than one)		
Easy bleeding		
Enlarged spleen		
Hepatitis		
Osteopenia or osteoporosis		
Difficulty controlling bowel		
Difficulty controlling bladder		
Numbness or tingling in arms or hands		
Numbness or tingling in legs or feet		
Weakness in arms or hands		
Weakness in legs or feet		
Recent change in coordination		
Recent change in ability to walk		
Spina bifida		
Latex allergy		

Explain "yes" answers here

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I hereby state that, to the best of my knowledge, my answers to the above questions are complete and correct.

Signature of athlete ______________ Signature of parent/guardian ______________ Date ______________

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Appendix A. (Continued.)

■ PREPARTICIPATION PHYSICAL EVALUATION
PHYSICAL EXAMINATION FORM

Name ______________________________ Date of birth ______________

PHYSICIAN REMINDERS

1. Consider additional questions on more sensitive issues
   - Do you feel stressed out or under a lot of pressure?
   - Do you ever feel sad, hopeless, depressed, or anxious?
   - Do you feel safe at your home or residence?
   - Have you ever tried cigarettes, chewing tobacco, snuff, or dip?
   - During the past 30 days, did you use chewing tobacco, snuff, or dip?
   - Do you drink alcohol or use any other drugs?
   - Have you ever taken anabolic steroids or used any other performance supplement?
   - Have you ever taken any supplements to help you gain or lose weight or improve your performance?
   - Do you wear a seat belt, use a helmet, and use condoms?
2. Consider reviewing questions on cardiovascular symptoms (questions 5–14).

EXAMINATION

Height Weight ☐ Male ☐ Female

BP / (/) Pulse Vision R 20/ L 20/ Corrected ☐ Y ☐ N

MEDICAL	**NORMAL**	**ABNORMAL FINDINGS**
Appearance • Marfan stigmata (kyphoscoliosis, high-arched palate, pectus excavatum, arachnodactyly, arm span > height, hyperlaxity, myopia, MVP, aortic insufficiency)		
Eyes/ears/nose/throat • Pupils equal • Hearing		
Lymph nodes		
Heart[a] • Murmurs (auscultation standing, supine, +/- Valsalva) • Location of point of maximal impulse (PMI)		
Pulses • Simultaneous femoral and radial pulses		
Lungs		
Abdomen		
Genitourinary (males only)[b]		
Skin • HSV, lesions suggestive of MRSA, tinea corporis		
Neurologic[c]		
MUSCULOSKELETAL		
Neck		
Back		
Shoulder/arm		
Elbow/forearm		
Wrist/hand/fingers		
Hip/thigh		
Knee		
Leg/ankle		
Foot/toes		
Functional • Duck-walk, single leg hop		

[a] Consider ECG, echocardiogram, and referral to cardiology for abnormal cardiac history or exam.
[b] Consider GU exam if in private setting. Having third party present is recommended.
[c] Consider cognitive evaluation or baseline neuropsychiatric testing if a history of significant concussion.

☐ Cleared for all sports without restriction

☐ Cleared for all sports without restriction with recommendations for further evaluation or treatment for ______________________________

____

☐ Not cleared
   ☐ Pending further evaluation
   ☐ For any sports
   ☐ For certain sports ______________________________
   Reason ______________________________

Recommendations ______________________________

____

I have examined the above-named student and completed the preparticipation physical evaluation. The athlete does not present apparent clinical contraindications to practice and participate in the sport(s) as outlined above. A copy of the physical exam is on record in my office and can be made available to the school at the request of the parents. If conditions arise after the athlete has been cleared for participation, the physician may rescind the clearance until the problem is resolved and the potential consequences are completely explained to the athlete (and parents/guardians).

Name of physician (print/type) ______________________________ Date ______________

Address ______________________________ Phone ______________

Signature of physician ______________________________, MD or DO

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Appendix A. (Continued.)

PREPARTICIPATION PHYSICAL EVALUATION
CLEARANCE FORM

Name ______________________________ Sex ☐ M ☐ F Age __________ Date of birth __________

☐ Cleared for all sports without restriction

☐ Cleared for all sports without restriction with recommendations for further evaluation or treatment for ______________________________

____

☐ Not cleared

- ☐ Pending further evaluation
- ☐ For any sports
- ☐ For certain sports ______________________________

  Reason ______________________________

Recommendations ______________________________

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I have examined the above-named student and completed the preparticipation physical evaluation. The athlete does not present apparent clinical contraindications to practice and participate in the sport(s) as outlined above. A copy of the physical exam is on record in my office and can be made available to the school at the request of the parents. If conditions arise after the athlete has been cleared for participation, the physician may rescind the clearance until the problem is resolved and the potential consequences are completely explained to the athlete (and parents/guardians).

Name of physician (print/type) ______________________________ Date __________

Address ______________________________ Phone __________

Signature of physician ______________________________, MD or DO

EMERGENCY INFORMATION

Allergies ______________________________

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Other information ______________________________

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Appendix A. (Continued.)

Condition	May Participate
Atlantoaxial instability (instability of the joint between cervical vertebrae 1 and 2)	Qualified yes
Explanation: Athlete (particularly if he or she has Down syndrome or juvenile rheumatoid arthritis with cervical involvement) needs evaluation to assess the risk of spinal cord injury during sports participation, especially when using a trampoline.[4–7]	
Bleeding disorder	Qualified yes
Explanation: Athlete needs evaluation.[8,9]	
Cardiovascular disease	
Carditis (inflammation of the heart)	No
Explanation: Carditis may result in sudden death with exertion.	
Hypertension (high blood pressure)	Qualified yes
Explanation: Those with hypertension >5 mm Hg above the 99th percentile for age, gender, and height should avoid heavy weightlifting and power lifting, bodybuilding, and high-static component sports (Fig 1). Those with sustained hypertension (>95th percentile for age, gender, and height) need evaluation.[10–12] The National High Blood Pressure Education Program Working Group report defined prehypertension and stage 1 and stage 2 hypertension in children and adolescents younger than 18 years of age.[10]	
Congenital heart disease (structural heart defects present at birth)	Qualified yes
Explanation: Consultation with a cardiologist is recommended. Those who have mild forms may participate fully in most cases; those who have moderate or severe forms or who have undergone surgery need evaluation. The 36th Bethesda Conference[12] defined mild, moderate, and severe disease for common cardiac lesions.	
Dysrhythmia (irregular heart rhythm)	Qualified yes
Long-QT syndrome	
Malignant ventricular arrhythmias	
Symptomatic Wolff-Parkinson-White syndrome	
Advanced heart block	
Family history of sudden death or previous sudden cardiac event	
Implantation of a cardioverter-defibrillator	
Explanation: Consultation with a cardiologist is advised. Those with symptoms (chest pain, syncope, near-syncope, dizziness, shortness of breath, or other symptoms of possible dysrhythmia) or evidence of mitral regurgitation on physical examination need evaluation. All others may participate fully.[13–15]	
Heart murmur	Qualified yes
Explanation: If the murmur is innocent (does not indicate heart disease), full participation is permitted. Otherwise, athlete needs evaluation (see structural heart disease, especially hypertrophic cardiomyopathy and mitral valve prolapse).	
Structural/acquired heart disease	
Hypertrophic cardiomyopathy	Qualified no
Coronary artery anomalies	Qualified no
Arrhythmogenic right ventricular cardiomyopathy	Qualified no
Acute rheumatic fever with carditis	Qualified no
Ehlers-Danlos syndrome, vascular form	Qualified no
Marfan syndrome	Qualified yes
Mitral valve prolapse	Qualified yes
Anthracycline use	Qualified yes
Explanation: Consultation with a cardiologist is recommended. The 36th Bethesda Conference provided detailed recommendations.[12,13,15–18] Most of these conditions carry a significant risk of sudden cardiac death associated with intense physical exercise. Hypertrophic cardiomyopathy requires thorough and repeated evaluations, because disease may change manifestations during later adolescence.[12,13,17] Marfan syndrome with an aortic aneurysm also can cause sudden death during intense physical exercise.[18] Athlete who has ever received chemotherapy with anthracyclines may be at increased risk of cardiac problems because of the cardiotoxic effects of the medications, and resistance training in this population should be approached with caution; strength training that avoids isometric contractions may be permitted.[19,20] Athlete needs evaluation.	
Vasculitis/vascular disease	Qualified yes
Kawasaki disease (coronary artery vasculitis)	
Pulmonary hypertension	
Explanation: Consultation with a cardiologist is recommended. Athlete needs individual evaluation to assess risk on the basis of disease activity, pathologic changes, and medical regimen.[21]	
Cerebral palsy	Qualified yes
Explanation: Athlete needs evaluation to assess functional capacity to perform sports-specific activity.	
Diabetes mellitus	Yes
Explanation: All sports can be played with proper attention and appropriate adjustments to diet (particularly carbohydrate intake), blood glucose concentrations, hydration, and insulin therapy. Blood glucose concentrations should be monitored before exercise, every 30 min during continuous exercise, 15 min after completion of exercise, and at bedtime.	
Diarrhea, infectious	Qualified no
Explanation: Unless symptoms are mild and athlete is fully hydrated, no participation is permitted, because diarrhea may increase risk of dehydration and heat illness (see fever).	
Eating disorders	Qualified yes
Explanation: Athlete with an eating disorder needs medical and psychiatric assessment before participation.	
Eyes	Qualified yes
Functionally 1-eyed athlete	
Loss of an eye	
Detached retina or family history of retinal detachment at young age	
High myopia	
Connective tissue disorder, such as Marfan or Stickler syndrome	
Previous intraocular eye surgery or serious eye injury	

Appendix B. Medical Conditions Affecting Sports Participation. (Reprinted with permission from Rice SG; American Academy of Pediatrics Council on Sports Medicine and Fitness. Medical conditions affecting sports participation. *Pediatrics*. 2008;121(4):841–848.)

Condition	May Participate
Explanation: A functionally 1-eyed athlete is defined as having best-corrected visual acuity worse than 20/40 in the poorer-seeing eye. Such an athlete would suffer significant disability if the better eye were seriously injured, as would an athlete with loss of an eye. Specifically, boxing and full-contact martial arts are not recommended for functionally 1-eyed athletes, because eye protection is impractical and/or not permitted. Some athletes who previously underwent intraocular eye surgery or had a serious eye injury may have increased risk of injury because of weakened eye tissue. Availability of eye guards approved by the American Society for Testing and Materials and other protective equipment may allow participation in most sports, but this must be judged on an individual basis.[22,23]	
Conjunctivitis, infectious	Qualified no
Explanation: Athlete with active infectious conjunctivitis should be excluded from swimming.	
Fever	No
Explanation: Elevated core temperature may be indicative of a pathologic medical condition (infection or disease) that is often manifest by increased resting metabolism and heart rate. Accordingly, during athlete's usual exercise regimen, the presence of fever can result in greater heat storage, decreased heat tolerance, increased risk of heat illness, increased cardiopulmonary effort, reduced maximal exercise capacity, and increased risk of hypotension because of altered vascular tone and dehydration. On rare occasions, fever may accompany myocarditis or other conditions that may make usual exercise dangerous.	
Gastrointestinal	Qualified yes
Malabsorption syndromes (celiac disease or cystic fibrosis)	
Explanation: Athlete needs individual assessment for general malnutrition or specific deficits resulting in coagulation or other defects; with appropriate treatment, these deficits can be treated adequately to permit normal activities.	
Short-bowel syndrome or other disorders requiring specialized nutritional support, including parenteral or enteral nutrition	
Explanation: Athlete needs individual assessment for collision, contact, or limited-contact sports. Presence of central or peripheral, indwelling, venous catheter may require special considerations for activities and emergency preparedness for unexpected trauma to the device(s).	
Heat illness, history of	Qualified yes
Explanation: Because of the likelihood of recurrence, athlete needs individual assessment to determine the presence of predisposing conditions and behaviors and to develop a prevention strategy that includes sufficient acclimatization (to the environment and to exercise intensity and duration), conditioning, hydration, and salt intake, as well as other effective measures to improve heat tolerance and to reduce heat injury risk (such as protective equipment and uniform configurations).[24,25]	
Hepatitis, infectious (primarily hepatitis C)	Yes
Explanation: All athletes should receive hepatitis B vaccination before participation. Because of the apparent minimal risk to others, all sports may be played as athlete's state of health allows. For all athletes, skin lesions should be covered properly, and athletic personnel should use universal precautions when handling blood or body fluids with visible blood.[26]	
HIV infection	Yes
Explanation: Because of the apparent minimal risk to others, all sports may be played as athlete's state of health allows (especially if viral load is undetectable or very low). For all athletes, skin lesions should be covered properly, and athletic personnel should use universal precautions when handling blood or body fluids with visible blood.[26] However, certain sports (such as wrestling and boxing) may create a situation that favors viral transmission (likely bleeding plus skin breaks). If viral load is detectable, then athletes should be advised to avoid such high-contact sports.	
Kidney, absence of one	Qualified yes
Explanation: Athlete needs individual assessment for contact, collision, and limited-contact sports. Protective equipment may reduce risk of injury to the remaining kidney sufficiently to allow participation in most sports, providing such equipment remains in place during activity.[22]	
Liver, enlarged	Qualified yes
Explanation: If the liver is acutely enlarged, then participation should be avoided because of risk of rupture. If the liver is chronically enlarged, then individual assessment is needed before collision, contact, or limited-contact sports are played. Patients with chronic liver disease may have changes in liver function that affect stamina, mental status, coagulation, or nutritional status.	
Malignant neoplasm	Qualified yes
Explanation: Athlete needs individual assessment.[27]	
Musculoskeletal disorders	Qualified yes
Explanation: Athlete needs individual assessment.	
Neurologic disorders	
History of serious head or spine trauma or abnormality, including craniotomy, epidural bleeding, subdural hematoma, intracerebral hemorrhage, second-impact syndrome, vascular malformation, and neck fracture.[4,5,28–30]	Qualified yes
Explanation: Athlete needs individual assessment for collision, contact, or limited-contact sports.	
History of simple concussion (mild traumatic brain injury), multiple simple concussions, and/or complex concussion	Qualified yes
Explanation: Athlete needs individual assessment. Research supports a conservative approach to concussion management, including no athletic participation while symptomatic or when deficits in judgment or cognition are detected, followed by graduated return to full activity.[28–32]	
Myopathies	Qualified yes
Explanation: Athlete needs individual assessment.	
Recurrent headaches	Yes
Explanation: Athlete needs individual assessment.[33]	
Recurrent plexopathy (burner or stinger) and cervical cord neuropraxia with persistent defects	Qualified yes
Explanation: Athlete needs individual assessment for collision, contact, or limited-contact sports; regaining normal strength is important benchmark for return to play.[34,35]	
Seizure disorder, well controlled	Yes
Explanation: Risk of seizure during participation is minimal.[36]	
Seizure disorder, poorly controlled	Qualified yes
Explanation: Athlete needs individual assessment for collision, contact, or limited-contact sports. The following noncontact sports should be avoided: archery, riflery, swimming, weightlifting, power lifting, strength training, and sports involving heights. In these sports, occurrence of a seizure during activity may pose a risk to self or others.[36]	

Appendix B. (Continued.)

Condition	May Participate
Obesity	Yes
Explanation: Because of the increased risk of heat illness and cardiovascular strain, obese athlete particularly needs careful acclimatization (to the environment and to exercise intensity and duration), sufficient hydration, and potential activity and recovery modifications during competition and training.[37]	
Organ transplant recipient (and those taking immunosuppressive medications)	Qualified yes
Explanation: Athlete needs individual assessment for contact, collision, and limited-contact sports. In addition to potential risk of infections, some medications (eg, prednisone) may increase tendency for bruising.	
Ovary, absence of one	Yes
Explanation: Risk of severe injury to remaining ovary is minimal.	
Pregnancy/postpartum	Qualified yes
Explanation: Athlete needs individual assessment. As pregnancy progresses, modifications to usual exercise routines will become necessary. Activities with high risk of falling or abdominal trauma should be avoided. Scuba diving and activities posing risk of altitude sickness should also be avoided during pregnancy. After the birth, physiological and morphologic changes of pregnancy take 4 to 6 weeks to return to baseline.[38,39]	
Respiratory conditions	
Pulmonary compromise, including cystic fibrosis	Qualified yes
Explanation: Athlete needs individual assessment but, generally, all sports may be played if oxygenation remains satisfactory during graded exercise test. Athletes with cystic fibrosis need acclimatization and good hydration to reduce risk of heat illness.	
Asthma	Yes
Explanation: With proper medication and education, only athletes with severe asthma need to modify their participation. For those using inhalers, recommend having a written action plan and using a peak flowmeter daily.[40–43] Athletes with asthma may encounter risks when scuba diving.	
Acute upper respiratory infection	Qualified yes
Explanation: Upper respiratory obstruction may affect pulmonary function. Athlete needs individual assessment for all except mild disease (see fever).	
Rheumatologic diseases	Qualified yes
Juvenile rheumatoid arthritis	
Explanation: Athletes with systemic or polyarticular juvenile rheumatoid arthritis and history of cervical spine involvement need radiographs of vertebrae C1 and C2 to assess risk of spinal cord injury. Athletes with systemic or HLA-B27-associated arthritis require cardiovascular assessment for possible cardiac complications during exercise. For those with micrognathia (open bite and exposed teeth), mouth guards are helpful. If uveitis is present, risk of eye damage from trauma is increased; ophthalmologic assessment is recommended. If visually impaired, guidelines for functionally 1-eyed athletes should be followed.[44]	
Juvenile dermatomyositis, idiopathic myositis	
Systemic lupus erythematosis	
Raynaud phenomenon	
Explanation: Athlete with juvenile dermatomyositis or systemic lupus erythematosis with cardiac involvement requires cardiology assessment before participation. Athletes receiving systemic corticosteroid therapy are at higher risk of osteoporotic fractures and avascular necrosis, which should be assessed before clearance; those receiving immunosuppressive medications are at higher risk of serious infection. Sports activities should be avoided when myositis is active. Rhabdomyolysis during intensive exercise may cause renal injury in athletes with idiopathic myositis and other myopathies. Because of photosensitivity with juvenile dermatomyositis and systemic lupus erythematosis, sun protection is necessary during outdoor activities. With Raynaud phenomenon, exposure to the cold presents risk to hands and feet.[45–48]	
Sickle cell disease	Qualified yes
Explanation: Athlete needs individual assessment. In general, if illness status permits, all sports may be played; however, any sport or activity that entails overexertion, overheating, dehydration, or chilling should be avoided. Participation at high altitude, especially when not acclimatized, also poses risk of sickle cell crisis.	
Sickle cell trait	Yes
Explanation: Athletes with sickle cell trait generally do not have increased risk of sudden death or other medical problems during athletic participation under normal environmental conditions. However, when high exertional activity is performed under extreme conditions of heat and humidity or increased altitude, such catastrophic complications have occurred rarely.[8,49–52] Athletes with sickle cell trait, like all athletes, should be progressively acclimatized to the environment and to the intensity and duration of activities and should be sufficiently hydrated to reduce the risk of exertional heat illness and/or rhabdomyolysis.[25] According to National Institutes of Health management guidelines, sickle cell trait is not a contraindication to participation in competitive athletics, and there is no requirement for screening before participation.[53] More research is needed to assess fully potential risks and benefits of screening athletes for sickle cell trait.	
Skin infections, including herpes simplex, molluscum contagiosum, verrucae (warts), staphylococcal and streptococcal infections (furuncles [boils], carbuncles, impetigo, methicillin-resistant *Staphylococcus aureus* [cellulitis and/or abscesses]), scabies, and tinea	Qualified yes
Explanation: During contagious periods, participation in gymnastics or cheerleading with mats, martial arts, wrestling, or other collision, contact, or limited-contact sports is not allowed.[54–57]	
Spleen, enlarged	Qualified yes
Explanation: If the spleen is acutely enlarged, then participation should be avoided because of risk of rupture. If the spleen is chronically enlarged, then individual assessment is needed before collision, contact, or limited-contact sports are played.	
Testicle, undescended or absence of one	Yes
Explanation: Certain sports may require a protective cup.[22]	

This table is designed for use by medical and nonmedical personnel. "Needs evaluation" means that a physician with appropriate knowledge and experience should assess the safety of a given sport for an athlete with the listed medical condition. Unless otherwise noted, this need for special consideration is because of variability in the severity of the disease, the risk of injury for the specific sports listed in Table 1, or both.

Appendix B. (Continued.)

The Sports Preparticipation Evaluation

Shane M. Miller and Andrew R. Peterson

Pediatrics in Review 2019;40;108

DOI: 10.1542/pir.2016-0216

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Femoroacetabular Impingement in Pediatric Patients

Evan D. Sheppard, MD,* Connor R. Read, MD,[†] Brad W. Wills, MD,* A. Reed Estes, MD*

*Department of Orthopaedic Surgery, University of Alabama at Birmingham, Birmingham, AL

[†]Department of Orthopaedic Surgery, University of Tennessee College of Medicine Chattanooga, Chattanooga, TN

Practice Gaps

1. To appropriately diagnose and care for patients with femoroacetabular impingement (FAI), clinicians should be able to identify the signs and symptoms of FAI, understand the pathoanatomy behind this condition, be able to order the appropriate radiologic evaluation, and provide appropriate management.
2. Clinicians should be aware of when to refer patients to a specialist for further care.

Objectives

After completing this article, readers should be able to:

1. Understand the epidemiology and causative factors associated with femoroacetabular impingement (FAI).
2. Identify the major anatomical factors that contribute to FAI.
3. Recognize clinical signs and symptoms of FAI.
4. Become proficient with basic physical examination of a patient with FAI.
5. Recognize classic radiographic findings of FAI.
6. Appropriately manage first-time presentation of FAI.
7. Have a general understanding of surgical options.
8. Know when to refer patients with FAI to a specialist for further care.

AUTHOR DISCLOSURE Drs Sheppard, Read, Wills, and Estes have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AP	anteroposterior
FAI	femoroacetabular impingement
LCP	Legg-Calve-Perthes disease
MRI	magnetic resonance imaging
SCFE	slipped capital femoral epiphysis

Abstract

Subacute, nontraumatic hip pain is often a diagnostic challenge. Femoroacetabular impingement (FAI) is a common cause of atraumatic hip pain that is poorly understood. FAI is a result of abnormal morphologic changes in either the femoral head or the acetabulum. FAI is more prevalent in people who perform activities requiring repetitive hip flexion, but it remains common in the general population. Evaluation begins with physical examination maneuvers to rule out additional hip pathology and provocation tests to reproduce hip pain. Diagnosis is often made by radiography or magnetic resonance imaging. Initial treatment is generally more conservative, featuring activity modification and physical therapy, whereas more aggressive treatment requires operative management.

INTRODUCTION

Patients with subacute, nontraumatic hip pain can represent a diagnostic challenge for the general pediatrician. The classic differential diagnosis includes Legg-Calve-Perthes disease (LCP), subacute slipped capital femoral epiphysis (SCFE), snapping hip syndrome, and iliotibial band tendonitis, among other entities. In the past 20 years, an entity known as femoroacetabular impingement (FAI) has become widely recognized as a common hip condition. FAI is a condition that results in morphologic changes to the head of the femur or rim of the acetabulum, generating pain and limiting range of motion. It is estimated that FAI is prevalent in more than 30% of the population. (1) Although less common in the pediatric population, certain pediatric conditions (ie, LCP, SCFE) predispose patients to the development of FAI. It has also been linked to the potential for idiopathic osteoarthritis in adulthood. (2) Since its recognition, there have been a growing number of diagnostic studies, radiographic measurements, and treatment options available. Appropriate referral to a specialist is important, but without adequate understanding of the pathoanatomy, physical examination findings, and radiographic evaluation results, primary care pediatricians risk either overreferring or underreferring children with this condition.

PATHOPHYSIOLOGY

FAI occurs as a result of abnormal morphologic changes in either the acetabulum or the head of the femur. These changes are classified into 3 categories: CAM lesions, pincer lesions, or mixed lesions. CAM deformities are changes in the femoral head and neck that cause the femoral head to lose its normally spherical shape (Fig 1A) and become shaped more like a rod or camshaft (Fig 1B). This causes the femoral head to contact the acetabulum during normal activities, particularly during flexion (Fig 1C). CAM lesions can be caused by a proximal physeal arrest (growth arrest at proximal femur growth plate), native femoral retroversion (rotation of the proximal femur), or a combination of the two. Relative femoral retroversion can lead to reduced internal rotation of the hip. CAM deformities can lead to anterosuperior labral injury. (3)

Pincer lesions relate to the prominence of the acetabular rim (Fig 1D). The result is that the acetabulum excessively covers the femoral head, mechanically blocking range of motion (Fig 1E). Essentially, it is an overreaching of the acetabular rim over the femoral head. Pincer lesions commonly place the labrum and, to a lesser degree, the cartilage at risk. In addition, pincer lesions increase the risk for contrecoup injury, an injury whereby the acetabulum acts as a fulcrum for the femur, producing posteroinferior subluxation, which may lead to damage of the posteroinferior and posteromedial chondral surfaces. (2) Pincer lesions are generally less common than CAM deformities.

FAI may also present as a mixed CAM-pincer lesion, also called a combination lesion. This type of lesion has features of both CAM deformity and pincer lesions. Patients with a history of proximal femur pathology, such as SCFE injuries, femoral neck fractures, and LCP, have been observed to have CAM lesions. (4) At a mean of 6.1 years of follow-up after fixation, approximately one-third of patients with SCFE injuries had positive impingement signs on physical examination, and 70% had evidence of FAI radiographically. (5) There was no correlation between the severity of the slip and FAI development. (5) LCP remains a risk factor for FAI development but is less common compared with SCFE. Collectively, these conditions predispose patients to hip impingement secondary to alterations in morphology of the femoral head and neck. Both SCFE and LCP provide explanations for FAI in the skeletally immature, however,

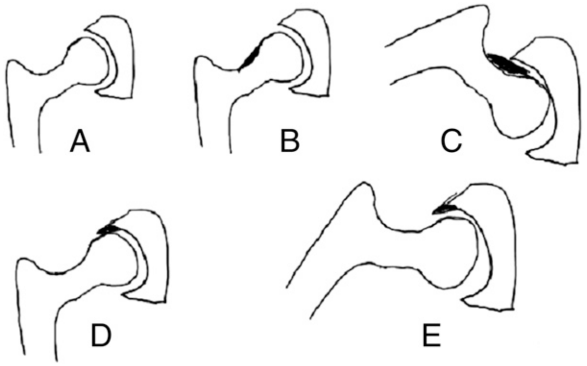

Figure 1. A. Normal hip anatomy. B. CAM deformity. C. Engagement of the CAM lesion. D. Pincer acetabular lesion. E. Pincer lesion impinging on the femoral neck.

other mechanisms have been proposed for FAI occurring in adolescents without a history of SCFE or LCP. FAI has been observed in adolescents who are athletes or participate in activities demanding repetitive hip flexion. One study followed skeletal maturation over 2 years in adolescent male soccer players (n = 63; mean age, 14 years). The authors found significant radiographic changes that correlated with the development of FAI. (6)

EPIDEMIOLOGY

FAI is a unique and often overlooked cause of hip pathology. Recently defined in the past 20 years, numerous studies have sought to fully describe this condition. Three studies have shown FAI to be more prevalent in males and that males were also more likely to have a more severe deformity compared with females. (7)(8)(9) In addition, FAI has a higher prevalence in young athletes. (8) CAM deformities have been found to be more common than pincer lesions. (7)(8) Multiple studies have shown that patients with more severe deformities are more likely to have an increased symptom burden, increased risk of hip dislocation, greater need for bilateral treatment, and higher prevalence of chondral pathology. (5)(6)(7)(9)(10)(11)(12)(13)

The prevalence of FAI in athletes has been shown to be greater than that in the general population. The risk is particularly higher in sports requiring repetitive hip flexion (ie, football, basketball, soccer). One meta-analysis found that high-level male athletes (ie, collegiate and professional) were 1.9 to 8 times more likely to develop FAI than were their male nonathlete counterparts. (13)(14) A review of the literature found that 95% of collegiate football players have at least 1 radiographic sign of FAI. (5) The prevalence of FAI in high-level basketball players was found to be as high as 89%. (13)

In general, FAI most commonly is found as a CAM deformity or a mixed CAM-pincer deformity and is more commonly seen in the pediatric and young adult population compared with middle-aged and older adults. It is more likely to affect males and individuals who are more frequently involved in activities involving repeated hip flexion. Injuries or developmental conditions resulting in trauma (eg, femoral neck fracture, SCFE) may also lead to the development of FAI.

TYPICAL PRESENTATION

FAI typically presents as deep anterior groin pain or anterolateral hip pain. Several authors describe the C sign demonstrated by young patients during the description of hip pain, where the cupping of the hand above the greater trochanter makes a *C* (Fig 2). (3)(14) Less commonly, patients describe lower lumbar back pain or posterior pelvic pain. Pain may also radiate to the anterior thigh and distally to the knee. The C sign has not been associated with groin injury or hernia pain. FAI pain is strongly associated with activities requiring repetitive hip flexion or rotation (eg, soccer, football, track) but may also be insidious in onset depending on the etiology. Similarly, pain may be present during times of prolonged hip flexion, such as lengthy car rides. Patients may experience popping, locking, or catching during physical activity.

PHYSICAL EXAMINATION

The physical examination for FAI is highly focused on ruling out other hip pathology, as there may be multiple causes of pain around the hip region. As always, it is important to compare with the contralateral extremity.

Initial assessment of gait may show signs of possible muscular imbalance. After gait assessment, it is important to palpate the thigh for tenderness, which may be attributed to a muscular origin of pain, or tenderness over the greater trochanter secondary to trochanteric bursitis. Next, hip range of motion is tested, and attention should be directed at which motions elicit pain. Internal rotation in a flexed hip may be limited with the presence of a CAM deformity. (15) Strength testing follows range of motion to better assess possible muscle imbalances. It is prudent to also evaluate the spine and knee as possible sources of pain.

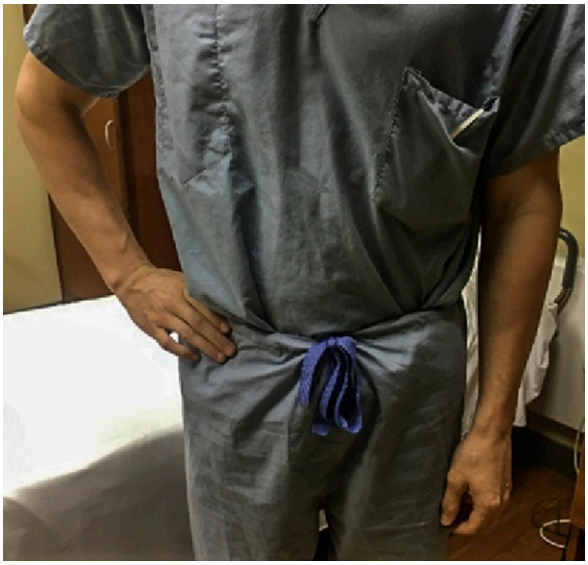

Figure 2. C sign commonly demonstrated coinciding with hip pain in femoroacetabular impingement.

There are several commonly used provocative tests for the hip; however, the best for FAI is the impingement test (Fig 3). (16) During this examination maneuver, the hip is flexed to 90° and then is adducted and internally rotated. This will commonly evoke pain in a patient with FAI. Hip extension with external rotation may also be used to check for posterior impingement. Pain with either of these maneuvers would indicate the need for further evaluation with imaging.

The Stinchfield test (Fig 4) is another examination that can further narrow down the diagnosis of hip pain. The patient actively flexes the leg to 30° to 45° while lying supine, and the examiner resists further flexion while applying pressure to the thigh just proximal to the knee. This is believed to load the anterosuperior labrum, reproducing groin pain. This test may also be positive, however, with hip flexor pathology.

Much of the physical examination is aimed at determining whether the pain is coming from an intra-articular source (as in FAI) or an extra-articular source. If the physical examination does not narrow down the source of pain, in a patient with a presentation otherwise consistent with FAI, an image-guided (ultrasonographic or fluoroscopic) intra-articular hip injection may be used to isolate the pain to an intra-articular cause. (17)(18)–(19) If the patient's symptoms are relieved by the injection, an intra-articular pathology is identified and further evaluation can commence to identify the pathology.

IMAGING

The initial imaging ordered for a patient with concern for FAI, or any other hip pathology, includes an anteroposterior (AP) pelvis and a frog-leg lateral of the hips. It is always important to compare imaging of both hips, although patients may present with bilateral disease. Figure 5 shows a normal, skeletally mature hip. When reviewing hip radiographs it is important to understand the normal anatomy. A good AP pelvis has the coccyx centered over the pubic symphysis and approximately 2 cm above it. Line A represents the acetabular roof, and line B represents the anterior wall of the acetabulum. Structure E is the radiographic teardrop, which is not a true anatomical landmark; however, if it is abnormal it can represent pathology of the acetabulum. Note the congruity and sphericity of the femoral heads. F represents normal joint space, and a decrease in this distance signifies cartilage loss.

CAM-type lesions will demonstrate a pistol grip deformity, where the proximal femur has a decreased offset and aspherical femoral head (Fig 6A). (20) Alpha angle is used to measure a CAM lesion. It is measured off the frog-leg lateral view by drawing a line between the center of the femoral head and the center of the femoral neck (Fig 6B). (21)

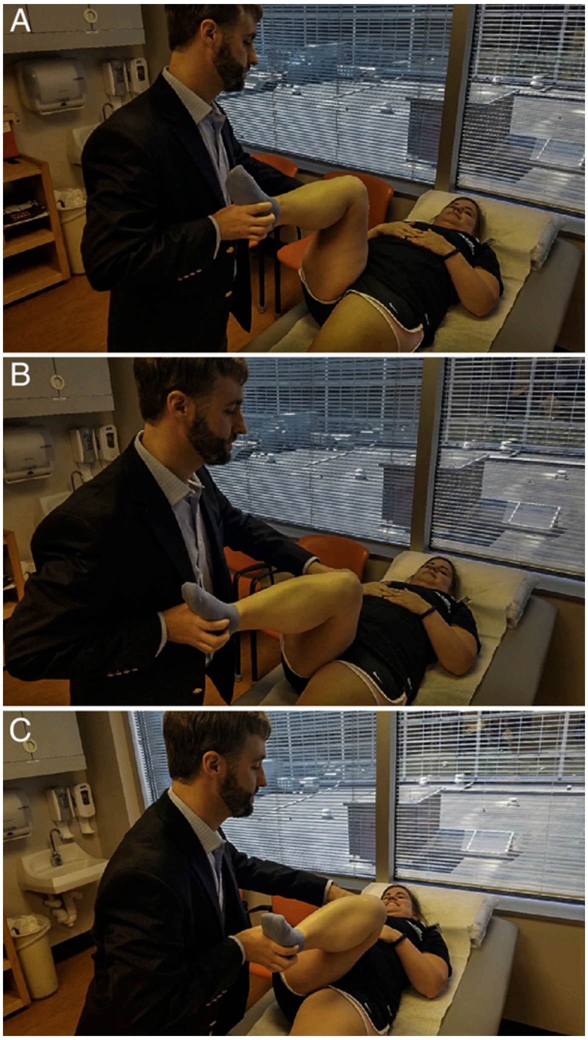

Figure 3. Physical examination technique for impingement. A. The hip is flexed to 90°. B. The hip is then internally rotated. C. The hip is then adducted while flexed and internally rotated.

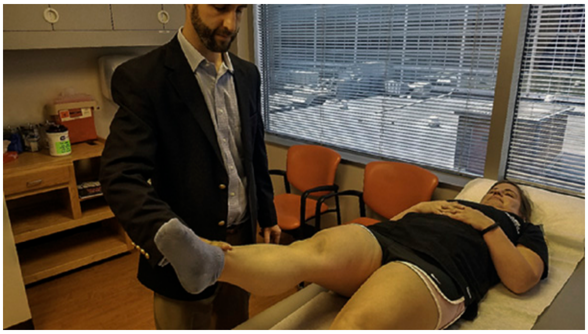

Figure 4. Stinchfield test. The patient actively flexes the leg to 30° to 45° while lying supine, and the examiner resists further flexion while applying pressure to the thigh just proximal to the knee.

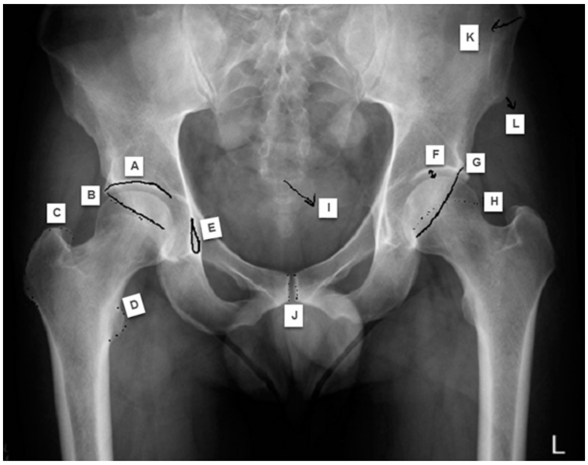

Figure 5. A normal, skeletally mature hip showing the acetabular roof (A), anterior wall of the acetabulum (B), greater trochanter (C), lesser trochanter (D), radiographic teardrop (E), normal joint space (F), posterior wall of the acetabulum (G), epiphysis in a young patient and epiphyseal scar in the skeletally mature (H), coccyx (I), pubic symphysis (J), anterosuperior iliac spine (K), and anteroinferior iliac spine (L).

Another line is drawn from the femoral head center to the area on the femoral neck where sphericity is lost. This point can be found by placing a circle around the femoral head and identifying the most proximal portion that lies outside of the circle. The angle between these 2 lines is then calculated. A normal value is less than 42°. (22)

Pincer deformity will demonstrate excessive overhang of the acetabulum (Fig 7), or acetabular protrusion, and retroversion of the acetabulum that will result in impingement. Typically, pincer deformity is identified from the AP pelvis from excessive coverage of the acetabulum, typically the anterosuperior acetabulum, or from identification of a crossover sign. The crossover sign is an indication of acetabular retroversion and is noted when radiographic lines of the anterior and posterior walls converge and cross before meeting at the most lateral portion of the acetabulum. (23) Other signs of acetabular retroversion include a prominent ischial spine where any portion of the ischial spine is found inside the pelvic brim on AP radiographs. (24)

Most surgeons use magnetic resonance imaging (MRI) with an arthrogram or computed tomographic scan for surgical planning to further evaluate the extent of the deformity and other associated hip pathology. The surgeon will review the coronal, sagittal, and axial views of the hip looking for chondral damage and labral pathology. If the primary care physician feels confident in the diagnosis and the patient is requesting surgical management, it is prudent to obtain an MRI to expedite the patient's management.

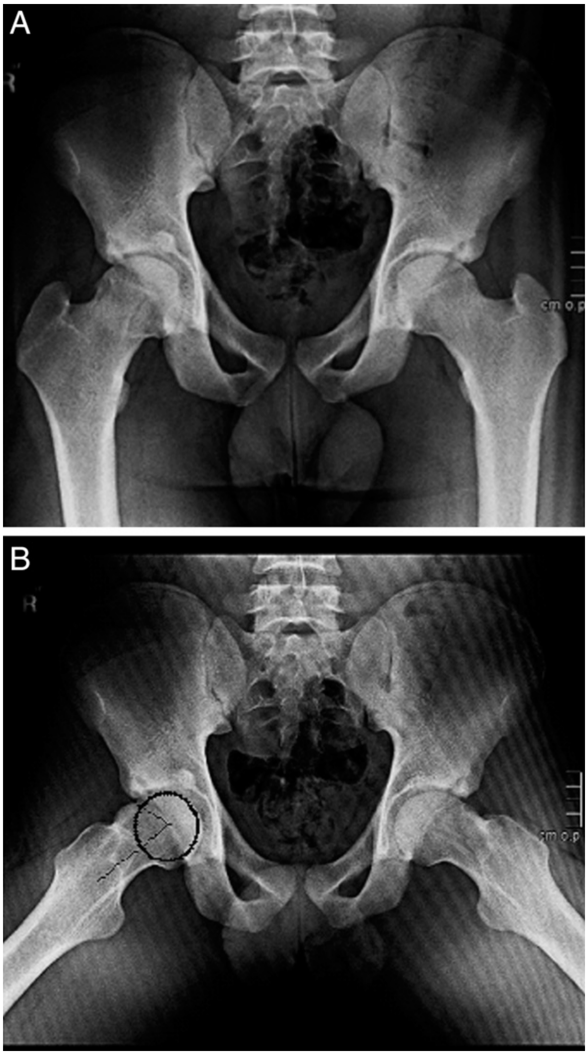

Figure 6. A. Anteroposterior radiograph of the hip. B. Frog-leg radiograph of the hip with demonstration of alpha angle measurement.

TREATMENT

Nonoperative Management

As with most musculoskeletal complaints, nonoperative management is often first-line treatment in mild FAI. Although there are few high-quality studies on nonoperative management for this condition, those that exist argue favorably for this treatment route. In Emara et al's cohort of 37 adult patients with FAI and a mild deformity treated nonsurgically with activity modification, 89% of patients had significant improvement at 2-year follow-up. (25) The first part of the protocol called for avoidance of excessive physical activity and the use of anti-inflammatory medications for 2 to 4 weeks during the acute inflammatory phase (when pain was acute and limiting). The next step involved physical therapy in the form of stretching exercises for 2 to 3 weeks, 20 to 30 minutes daily, that focused on improving hip flexibility, mainly by

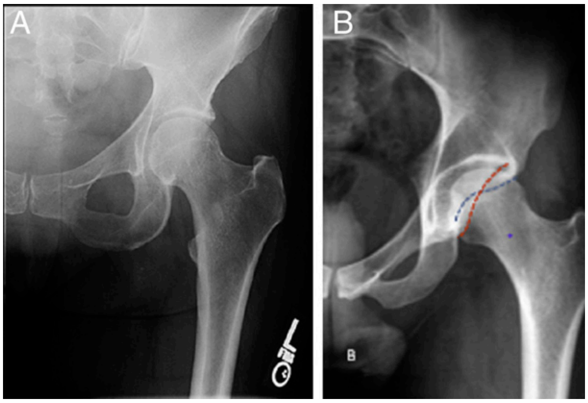

Figure 7. A. Pincer lesion represents acetabular overhang. B. Crossover sign represents acetabular retroversion.

external rotation and abduction in extension and flexion. The final step involved educating patients on safe range of motion to avoid impingement and teaching patients how to adapt their restrictions to their activities of daily living. They were taught to avoid positions between maximum internal and external rotation and to avoid full flexion. They were restricted also from running and cycling long term.

Intra-articular injections serve as another nonoperative modality in treating FAI in conjunction with or after physical therapy and activity modification. The added benefit of an intra-articular injection is the diagnostic as well as therapeutic value. (26) A systematic review by Khan et al (26) found that hyaluronic acid injections achieved up to 1 year of symptom relief. This review showed less success with corticosteroid injections.

Unfortunately, the nonoperative data were gathered from young-adult and adult populations, so the role of nonoperative management in pediatric FAI is not well delineated. More research needs to be conducted in this field.

Operative Management

Patients who have failed nonoperative therapies, have more severe bone deformity, or have chondrolabral pathology (labral tear or osteochondral lesion) on MRI often necessitate referral to an orthopedist for surgical consideration. (27) Operative management of patients with symptomatic FAI aims to address the pathology of the chondrolabral surfaces and underlying bone deformity. The type of surgery heavily depends on the severity of the deformity and MRI findings.

Historically, surgical dislocation was used to manage FAI. (28) This method safely exposed the proximal femur and acetabulum without compromising the blood supply to the neck. Early studies reported moderate success (68%–82%). (29) Complications rates were approximately 9%. (30) Open treatment allows for good visualization of the femoral neck and acetabulum and allows the surgeon to address lesions of both easily. Periacetabular osteotomies are indicated in patients with severe acetabular retroversion. In small case reports, good to excellent results in 90% of patients at a minimum of 2 years of follow-up were noted. (31)

As early as the 1970s, hip arthroscopy was used to treat labral pathology in the hip. As FAI became better understood and recognized, arthroscopy was used to attempt to treat this pathology. Hip arthroscopy is becoming the treatment of choice in the pediatric population. (27)(32) Arthroscopic management of CAM deformities begins with a fluoroscopic examination to identify areas of dynamic impingement. An arthroscope is then introduced into the joint and the pathology assessed. If a CAM lesion is present, a burr and a shaver are used to resect the lesion. The arthroscopic burr is used for acetabular rim resection as well. If there is labral pathology, suture anchors are used to repair the labrum if amenable. Cartilage lesions can be assessed and treated with microfracture if found to be full thickness. (27)(32) Microfracture entails taking a small pointed instrument and creating holes in the subchondral bone with the hope that the ensuing bleeding brings stem cells to the surface and to create a scar of fibrocartilage to replace the damaged hyaline cartilage. Once finished, the hip is put through another dynamic intraoperative examination under fluoroscopy. Currently there is no established postoperative rehabilitation protocol and, thus, the decision depends on an individual surgeon's preference.

Results of arthroscopic treatment of FAI are encouraging. There have been several studies demonstrating early success of these procedures, measured by improvement in the modified Harris Hip Score and Hip Outcomes Score. (27)(32) In a small study of 34 patients younger than 18 years, 78% returned fully to sports and saw an improvement from 77 to 94 (of 100) in the modified Harris Hip Score. (33) The complication rate reported in a large cohort of patients younger than 18 years was 1.8%. (33) Transient pudendal nerve palsy, suture abscess, and intra-articular instrument breakage were the most common complications, and no growth disturbances were observed.

Operative versus Nonoperative Treatment

There are few data comparing surgical and nonsurgical treatment in the pediatric population. A recent systematic review assessed 29 papers looking at outcomes after surgical and nonsurgical treatment of FAI. These studies were mostly level IV evidence. They encompassed both American and European populations, and the average age was 34 years. They found that in symptomatic patients, those treated surgically had better functional score outcomes. (34)

WHEN TO REFER TO A SPECIALIST

As with any subacute complaint, it is important to know which patients require referral to a subspecialist for operative consideration and which patients warrant conservative measures first. Evaluation of these patients is important to obtain an accurate diagnosis. Appropriate physical examination findings, such as limited hip internal rotation with the hip flexed or pain with anterior and posterior impingement testing, should alert the clinician to consider FAI as a possible diagnosis. Radiographs should then be obtained, and if results are concerning for FAI, an MRI can be ordered. Once the diagnosis is made, physical therapy, activity modification, and hip injections should be tried. If these conservative measures fail, surgical intervention will likely be warranted and referral to a sports medicine or pediatric orthopedist must be considered.

Summary

- Based on level of evidence IIa, femoroacetabular impingement (FAI) is a common enough cause of hip pathology and should be included in the differential diagnosis in patients with subacute, nontraumatic hip pain. (1)(2)(3)(4)(5)(6)(7)(8)
- Based on level of evidence IV, a good history and physical examination are beneficial in identifying higher-risk patients, elucidating features consistent with FAI pain, and assessing limited range of motion or positive impingement findings on physical examination. A good history and physical examination will also help rule out other causes of hip pathology, such as iliopsoas tendonitis, slipped capital femoral epiphysis, or Legg-Calve-Perthes disease. (2)(13)(15)(16)(17)
- Based on level of evidence IIa, initial imaging should be completed with radiography, which may reveal 1 or a combination of lesions specific to FAI: CAM lesion, pincer lesion, or mixed. (17)(18)(19)(20)(21)
- Based on level of evidence IIa, conservative management may be offered first and should consist of activity restrictions and anti-inflammatory medications. Intra-articular injections may be useful. (24)(25)
- Based on level of evidence V, referral to a specialist should occur when the patient with FAI fails conservative management. (26)(27)(28)(29)(30)(31)(32)(33)(35)(36)(37)

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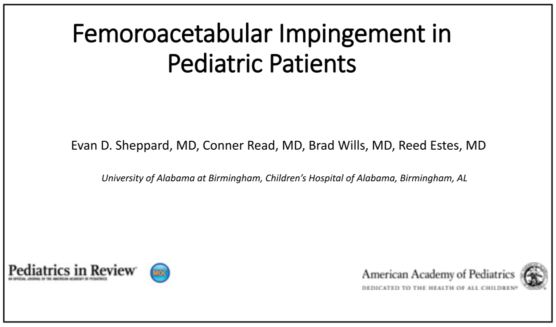

Femoroacetabular Impingement in
Pediatric Patients

Evan D. Sheppard, MD, Conner Read, MD, Brad Wills, MD, Reed Estes, MD

University of Alabama at Birmingham, Children's Hospital of Alabama, Birmingham, AL

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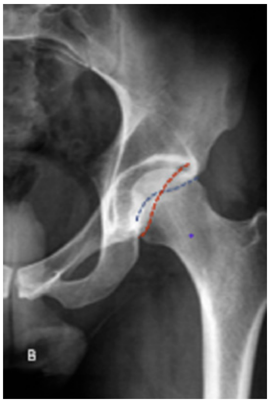
1. A 14-year-old boy is seen in the clinic for a sports preparticipation physical. He is in good health and plays for his school soccer team. He reports pain around his right hip but denies any history of trauma. From the following signs and symptoms, which additional one should lead the clinician to consider a diagnosis of femoroacetabular impingement (FAI) in this patient?
   - A. Hyperflexibility of the hip joint.
   - B. Numbness in the anterior thigh.
   - C. Popping or catching during activity.
   - D. Pain associated with repetitive hip extension activities.
   - E. Weakness in the quadriceps muscle.
2. In the patient described in the vignette in question 1, physical examination is performed including gait assessment, hip range of motion, strength testing, and assessment of the spine and knee. A diagnosis of FAI is suspected. Which of the following provocative maneuvers is the best to confirm the diagnosis of FAI in this patient?
   - A. Flexion, abduction, external rotation (FABER) test.
   - B. Impingement test.
   - C. Log roll test.
   - D. Stinchfield test.
   - E. Straight-leg raise test.
3. The patient in question 1 complained of pain while the examiner performed the impingement provocation test. Which of the following imaging studies is the most appropriate initial diagnostic test that should be obtained to confirm the diagnosis of FAI?
   - A. Bone scan.
   - B. Hip computed tomography.
   - C. Magnetic resonance imaging of the hips.
   - D. Radiographs in anteroposterior pelvis and frog-leg lateral of both hips.
   - E. Ultrasonography of the affected hip.
4. A 14-year-old soccer player was brought to the sports medicine clinic for evaluation of hip pain. The findings from the history and physical examination, including the provocative maneuvers, were consistent with FAI. A hip radiograph was obtained and is shown in the photograph below. The radiologist has drawn some lines over the radiograph. Which of the following represents the best interpretation of what the red dashed line represents in the radiograph of this patient?



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A. Crossover sign (acetabular retroversion).
B. Pincer lesion (acetabular overhang).
C. Pistol grip deformity.
D. Prominent ischial spine.
E. Slipped capital femoral epiphysis.

5. The patient described in the vignette in question 4 is diagnosed as having FAI. He was started on a nonoperative management protocol that included activity modification, anti-inflammatory medications, physical therapy, and intra-articular injections of hyaluronic acid. The patient was seen in follow-up for 1 year. Today he reports recurrence of his symptoms over the past few months after a period of partial relief. Which of the following surgical techniques is most likely to be considered at this point by the treating orthopedic surgeon in this patient?

A. D-rotation osteotomy of the hip.
B. Hip arthroscopy.
C. Internal fixation of the hip.
D. Periacetabular osteotomy.
E. Surgical dislocation.

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Index of Suspicion

1 New-Onset Seizures in a 16-year-old Girl Recently Emigrated from Africa

Rachel Cafferty, MD,[†] Cynthia Howard, MD, MPHTM,[†] Rahul Kaila, MD[‡]

[†]Department of Pediatrics, and [‡]Department of Pediatric Emergency Medicine, University of Minnesota Masonic Children's Hospital, Minneapolis, MN

AUTHOR DISCLOSURE Drs Cafferty, Howard, and Kaila have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

EDITOR'S NOTE

After Match Day this month, some senior medical students will be heading off for global health rotations. Some residents and practicing physicians are finalizing plans for summer service-learning trips in countries far from home. Meanwhile, pediatric offices in North America are increasingly seeing recent immigrants who might carry conditions that seem uncommon. To help prepare all readers in all parts of the world, *Index of Suspicion* highlights cases this month that are particularly relevant to readers interested in global health.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A 16-year-old previously healthy girl with recent international emigration with refugee status from Tanzania presents via emergency medical services (EMS) with new-onset seizurelike activity. She had spent the 48 hours immediately before presentation traveling from Tanzania to the United States via Switzerland, with minimal sleep. The EMS was called to the home after the family found the girl lying on the floor covered in vomit with shaking movements of her extremities and eyes rolled back. She is without seizure activity and is not postictal in appearance when EMS arrives. She is noted to have a history of malaria several years earlier (treated and without recurrence), but no other medical problems. She has no personal or family history of seizure disorders, she is not taking medications, and there is no concern for illicit substance abuse, medication ingestion, or precipitating trauma. She has had no recent fever, headache, abdominal pain, vomiting, diarrhea, or other concerns.

During transport to the emergency department (ED) she receives a dose of ondansetron. On arrival, her temperature is 98.4°F (36.9°C), respirations are 16 breaths/min, heart rate is 87 beats/min, blood pressure is 133/84 mm Hg, and oxygen saturation is 100% on room air. Physical examination reveals no distress. Her head is normocephalic and atraumatic. Her neck is supple without meningismus. Her chest is clear to auscultation, with normal heart sounds. Her abdomen is nondistended, nontender, and without organomegaly. Her skin is clear, without rash or petechiae. Results of a complete neurologic examination are

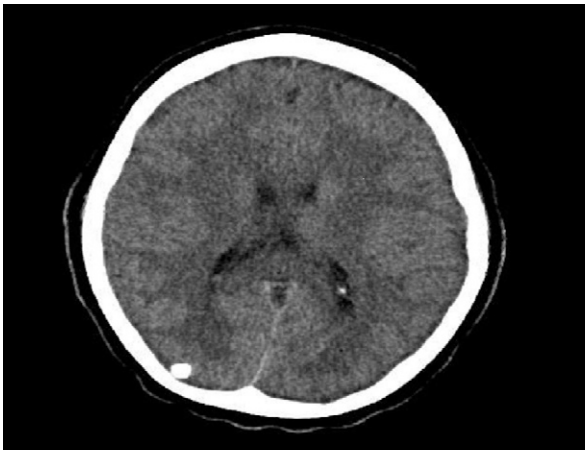

Figure 1. Computed tomographic scan of the head without contrast. There is a 0.7-cm benign-appearing right occipital lobe calcification without associated mass effect.

normal, her Glasgow Coma Scale score is 15, and her glucose level is 120 mg/dL (6.7 mmol/L). The values for complete blood cell count (with differential count), serum electrolytes, blood urea nitrogen, creatinine, liver enzymes, and lipase are within normal limits. A computed tomographic (CT) scan of the head without contrast reveals a 0.7-cm benign-appearing right occipital lobe calcification without associated mass effect of uncertain etiology and significance (Fig 1). After imaging, the girl begins to actively seize, with generalized tonic-clonic activity and an episode of urinary incontinence. She receives 1 mg of lorazepam intravenously, oxygen via a nonrebreather mask, and, subsequently, a loading dose of levetiracetam due to ongoing seizure activity. During hospitalization, routine electroencephalography is performed and the results are normal during a state of wakefulness. Magnetic resonance imaging (MRI) of the brain and entire spine with and without contrast reveals the diagnosis.

DISCUSSION

Differential Diagnosis

The differential diagnosis for this adolescent's presentation includes neurocysticercosis, central nervous system (CNS) toxoplasmosis, CNS cryptococcosis, tuberculosis meningitis or CNS tuberculosis, cerebral amebiasis, neurosarcoidosis, healed brain abscess, CNS tumors, healed infarct or hematoma, or benign calcifications with unexplained seizure etiology.

Actual Diagnosis

Magnetic resonance imaging of the brain and entire spine with and without contrast was performed during this hospitalization, which was significant for a 5-mm peripherally enhancing lesion with surrounding vasogenic edema in the left inferior lateral frontal lobe, consistent with a colloidal vesicular neurocysticercosis lesion (Fig 2). An additional nonenhancing lesion in the right occipital lobe was correlated with the area of calcification on previous CT. No abnormal signal was present in the spinal cord.

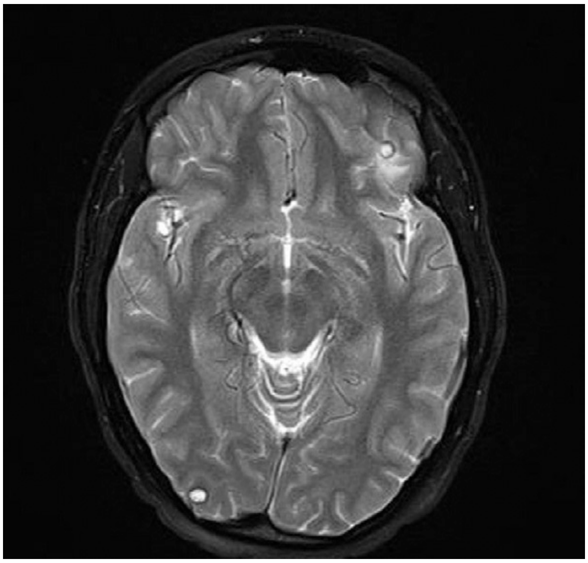

Figure 2. Magnetic resonance imaging of the brain with contrast. There is a 5-mm peripherally enhancing lesion with surrounding vasogenic edema in the left inferolateral frontal lobe, likely representing a colloidal vesicular neurocysticercosis lesion. An additional nonenhancing lesion with similar signal characteristics in the right occipital lobe is present, matching the area of calcification on a previous computed tomographic scan.

Patient Course

Throughout hospitalization the patient was continued on maintenance levetiracetam therapy. A dilated ophthalmologic examination was performed, which was negative for ophthalmic cysticercosis. Cysticercosis serology and stool ova and parasites examination sent to the Centers for Disease Control and Prevention (CDC) were negative. Due to concern for neurocysticercosis despite negative serologic testing (1) the patient was treated with cysticidal therapy (albendazole) with concomitant corticosteroids. She did not receive combination therapy with praziquantel given that her disease was not multicystic in nature. The patient continues on maintenance antiepileptic medications and has remained seizure-free.

The Condition

Taenia solium produces an intestinal infection caused by adult tapeworms that occurs after ingestion of contaminated pork. (2) The presence of *T solium* cysts in the brain is termed *neurocysticercosis*, the most serious form of the disease. Seizures are the most common manifestation of neurocysticercosis, present in 70% to 90% of symptomatic patients. (1) In endemic regions, neurocysticercosis is regarded as the "great imitator," with the ability to mimic nearly all neurologic disorders. (3) Confusion, poor attention, balance difficulties, hydrocephalus, chronic meningitis, cranial nerve abnormalities, and stroke are rare but may occur. Symptoms depend on the number, location, size, and stage (viable, degenerating, or calcified) of cysticerci. Live cysts do not incite a major inflammatory reaction; cyst degeneration releases parasite antigens and may result in an acute inflammatory response with significant morbidity. Necrotic larvae may resorb or calcify and produce local scarring, which serves as a focus for seizure activity. (1)

The World Health Organization recently named *T solium* the "food-borne parasite of greatest global concern." (4) Infection rates of cysticercosis (including neurocysticercosis) are highest in developing countries with free-roaming pigs and poor sanitation throughout Latin America, Asia, and Africa. (1) Neurocysticercosis is the most frequent preventable cause of epilepsy in developing nations, accounting for an estimated 30% of cases where the parasite is endemic. (5) Although *T solium* infection is not endemic in the United States and local transmission is low, increases in immigration from endemic regions has led to a higher incidence of neurocysticercosis locally. (3) Of patients presenting to an ED in the United States with seizures, 2% to 10% are ultimately diagnosed as having neurocysticercosis. (6)

Neurocysticercosis is challenging to diagnose, particularly in resource-limited countries worldwide, where CT and MRI are not readily available. Diagnosis of neurocysticercosis usually requires CT or MRI, as well as serologic testing (by enzyme-linked immunoelectrotransfer blot [EITB] or commercial enzyme-linked immunoassays). The EITB is highly sensitive (94% sensitivity) in cases of neurocysticercosis in which 2 or more lesions are present. (7) However, EITB has low sensitivity (28%) in cases of single lesion disease or calcified cysts. (7) In cases of clinically suspected and MRI-proven neurocysticercosis, anticysticercus antibodies may be positive in less than 50% of patients. (8) Imaging of the CNS demonstrates a contrast-enhancing ring around a cyst due to local inflammation and resultant edema. A single enhancing nodule is more commonly found in individuals younger than 30 years, and inflammation is more exaggerated in children. (3)

Treatment/Management

Treatment of neurocysticercosis consists of anticonvulsant therapy (if indicated), corticosteroids, antihelminthic treatment, and, at times, neurosurgical intervention. The 2017 Infectious Diseases Society of America and American Society of Tropical Medicine and Hygiene guidelines on the diagnosis and treatment of neurocysticerosis recommend albendazole monotherapy (15 mg/kg per day divided into 2 daily doses) for 10 to 14 days in patients with 1 to 2 viable parenchymal cysticerci. (9) Combination therapy with both albendazole and praziquantel for the treatment of multicystic intraparenchymal neurocysticercosis has demonstrated superior results without increased adverse effects. (10) Caution must be taken when initiating antihelminthic treatment because larval death provokes an inflammatory response that may result in increased symptoms acutely. As a result, co-administration of corticosteroids that cross the blood-brain barrier (eg, dexamethasone) is usually indicated. Antihelminthic treatment is not beneficial in cases of calcified cysts (dead parasite).

Recurrence of seizures after initiation of treatment occurs at a rate of 10% to 34% in patients with calcified lesions, 13% to 48% in individuals with a single granuloma, and 54% in those with multicystic disease. (3) However, many individuals tolerate weaning off of anticonvulsant therapy after antihelminthic treatment is complete.

CONCLUSION

Neurocysticercosis, the leading cause of epilepsy worldwide, is endemic in many of the countries worldwide from which individuals emigrate to the United States, resulting in an increase of cases locally. (6) Live cysts in the brain are often asymptomatic, but cyst degeneration releases parasite antigens and incites an acute inflammatory response, which can provoke neurologic sequelae. Before international travel, CDC guidelines state that US-bound refugees should be treated with a single dose of albendazole and praziquantel for the treatment of presumed parasite infection. Predeparture treatment was confirmed for our patient, which likely initiated the cysticidal activity in the brain resulting in inflammation and edema and provoking first-time seizures. Although aimed at treatment of intestinal parasitic disease, knowing that provocation of neurologic symptoms may result after predeparture treatment should raise awareness in all providers that new-onset seizures occurring in immigrant refugee populations shortly after arrival in the United States are highly suspicious for neurocysticercosis.

Lessons for the Clinician

- Neurocysticercosis, the leading cause of epilepsy worldwide, is now more commonly seen in the United States as individuals emigrate from areas in which *Taenia solium* is endemic.
- Neurocysticercosis is difficult to diagnose and requires a high clinical suspicion. Enzyme-linked immunoelectrotransfer blot is highly sensitive for cases in which 2 or more central nervous system lesions are present but has low sensitivity in cases of single-lesion disease or calcified cysts.
- Live cysts are often asymptomatic. Cyst degeneration incites a local acute inflammatory response, which can provoke seizures.
- Predeparture treatment, as recommended by the CDC for the treatment of intestinal parasitic disease, may initiate cysticidal activity in the central nervous system, resulting in neurologic sequelae.
- Albendazole monotherapy is recommended for patients with 1 to 2 viable parenchymal cysticerci. Combination therapy with albendazole and praziquantel has been shown to be beneficial for multicystic intraparenchymal neurocysticercosis. Co-administration of corticosteroids with antihelminthic medication counters the host inflammatory response that occurs with larval death and is beneficial in decreasing the occurrence of seizures when starting therapy.

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Fever, Chills, and Abdominal Pain in a 4-year-old Girl

Juan R. Barrón Alemañy, MD, MPH,* Tamera Akarah, MD†

*Department of Pediatrics, Comer Children's Hospital, Pritzker School of Medicine, and
†Department of Family Medicine, Northshore University Health System, University of Chicago,
Evanston, IL

AUTHOR DISCLOSURE Drs Barrón Alemañy and Akarah have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 4-year-old girl presents to a pediatrician's office for evaluation of fever and chills. The mother reports that the patient has not been feeling well for the past couple of days, with nausea, vomiting, decreased appetite, generalized abdominal pain, and decreased urine output. Medical and family histories are noncontributory. The mother and patient recently traveled to India for their yearly 1-month visit to family members and returned approximately 2 to 3 weeks ago. The primary care physician evaluated the patient with a rapid streptococcal test and a throat culture for streptococcal pharyngitis, a rapid antibody test for infectious mononucleosis, and a blood smear for malaria; all of these results were negative. On day 5 of illness, the patient is brought again to the primary care physician's office and is subsequently sent to the emergency department for further management. The patient has continued with persistent fevers and chills for the past 5 days. Her maximum measured temperature was 103°F (39.4°C) at home, and the mother reports that fevers subside with antipyretic use. On physical examination the patient is noted to have unremarkable vital signs, looks well, and has no significant findings. Therefore, the patient is discharged with instructions for supportive care for a likely viral illness given that her mother has tested positive for Epstein-Barr virus. Further blood test results eventually yield the diagnosis.

DISCUSSION

Multiple things have to be taken into consideration when a patient presents with these symptoms. Her travel history is important to the timing of presentation. Known diseases that are endemic to South Asia include malaria, dengue, chikungunya, enteric fevers, and leptospirosis, among others. All of these infections can present with fevers, and one thing that can help differentiate them could be the timing of incubation. When thinking of incubation in less than 10 days, we think more of infections such as dengue fever and chikungunya. These can also be accompanied by headaches, rash, myalgia, arthritis, and hemorrhages. Malaria and leptospirosis have an incubation period of days to months. The description of the fevers and constitutional symptoms can also be helpful. With malaria we can see waxing and waning of fevers, accompanied by myalgia, anemia, nausea, vomiting, diarrhea, and abdominal pain. When there is a known exposure to animal urine or contaminated water, leptospirosis is high on the differential diagnosis.

Our patient presented with these symptoms at least 3 weeks after returning from travel, which helped us rule out some of these infections. Her peripheral blood smear was negative for malaria, and the preliminary report for the blood culture revealed growth of gram-negative rods.

Diagnosis

The blood culture's final identification revealed the organism to be *Salmonella typhi*.

Typhoid fever is not usually seen in the United States given that it is not an endemic area. This case pointed out that we should always take into consideration different types of etiologies for persistent fevers, reminding us of how important travel history is in all patients and their families.

Reviewing more about *S typhi,* this species has humans as the only host and reservoir, unlike other common types such as *Salmonella paratyphi*, which can infect animals. The transmission is mainly by consumption of contaminated food or water and occasionally by direct fecal-oral route. After ingestion and reaching the small intestine, the bacteria penetrate the intestinal mucosa and are ingested by macrophages, where they live and multiply. Afterward they reach the mesenteric lymph nodes and reach the bloodstream via the thoracic duct, causing primary bacteremia. The bacterium continues seeding and multiplying in the spleen, liver, gall bladder, bone marrow, and lymph nodes. It is here where they reside during the incubation period, which varies from 3 to 60 days. After multiplication in large numbers, bacteria spill into the bloodstream, creating the secondary bacteremia, and this prompts the initiation of clinical symptoms.

The patient's clinical manifestations include persistent fevers, abdominal pain, nausea, vomiting, diarrhea in children, constipation in adults, headache, malaise, and anorexia. Some cases may present with an exanthema characterized by "rose spots" on the chest, abdomen, and back. In more complicated cases, extraintestinal manifestations may occur, including melena, intestinal abscesses, intestinal perforation, altered mental status, meningitis, coma, and death.

Some patients become chronic carriers of the bacterium, estimated to be approximately 2% to 5% of those who had infection. This is defined as excretion of the organism in stool or urine for more than 12 months after an acute infection. The bacteria persist in the biliary tract after symptoms resolve.

Typhoid fever is usually treated with a single antibiotic drug, but it depends on how severe the presentation of illness is, whether there are any local resistance patterns, the feasibility of taking oral medications, the clinical setting, and available resources. The usual choices are fluoroquinolones, with a duration of 7 to 10 days; third-generation cephalosporins, lasting 10 to 14 days; and azithromycin, prescribed for 5 to 7 days. Also used agents are chloramphenicol (duration, 2–3 weeks), ampicillin, or trimethoprim-sulfamethoxazole (duration of both, 10–14 days); but these are less frequently used given the prevalence of resistance. For patients with prolonged fever who require parenteral therapy, ceftriaxone is recommended as empirical therapy. Usually, defervescence is seen by day 4 or 5 of parenteral treatment. Once symptoms improve and susceptibilities have been tested, switching to oral antibiotics is appropriate.

The main mechanism of prevention would be avoiding ingestion of water and food in areas of poor sanitation and personal hygiene. There is also an indication for typhoid vaccination in travelers and individuals with a high risk of exposure. At the moment, there are 2 available vaccines: oral live vaccine and Vi capsular polysaccharide vaccine. Neither is completely effective against *S typhi;* therefore, routine vaccination is not recommended in the United States according to the Centers for Disease Control and Prevention (CDC) guidelines. Vaccination is recommended for those who are planning to travel to endemic regions, individuals who are in close contact with known carriers, and for those whose work exposes them to *S typhi*, such as microbiologists and laboratory workers.

Patient Course

Our patient was admitted for intravenous antibiotic therapy and was started on ceftriaxone, 1 g twice a day. Her fevers and symptoms continued for the first 4 days of hospitalization. By the fifth day she started having improvement of symptoms without nausea, vomiting, or diarrhea. Her fevers also started to subside by day 5. The blood culture sensitivities were also back and demonstrated susceptibility to trimethoprim-sulfamethoxazole. After being afebrile for 24 hours, the patient was transitioned to oral antibiotics for a total of 14 days of treatment. Of note, the patient's mother also tested positive for *S typhi* on blood culture and was started on oral antibiotics.

After discharge, the patient followed up with her pediatrician and continued to be afebrile and denied any recurrent symptoms of diarrhea or vomiting. She continued to have positive stool cultures for *Salmonella* and is now considered to be a convalescent carrier.

Lessons for the Clinician

- Consider typhoid fever in patients with persistent fevers and a known travel history to resource-limited countries where these infections are endemic.
- Treatment should be started as quickly as possible to avoid severe complications such as intestinal abscesses, perforation, meningitis, coma, or death secondary to *Salmonella typhi* (typhoid fever).
- Knowing who is at higher risk to become infected with *S typhi* is important when discussing vaccination for the patient and/or family members.

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Hepatosplenomegaly with Hyperpigmentation in a 6-year-old Girl

Suneel Mundkur, DCH DNB,* Sowmya Shashidhara, MD,*
Shrikiran Hebbar, MD,* Shravan Kanaparthi, MD*

**Department of Pediatrics, Women and Child Block, Kasturba Medical College, Manipal Academy of Higher Education, Madhav Nagar, Manipal, Karnataka, India*

AUTHOR DISCLOSURE Drs Mundkur, Shashidhara, Hebbar, and Kanaparthi have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 6-year-old girl of eastern Himalayan origin presents with a 1-year history of recurring fever and abdominal pain. The fever is intermittent and high grade, associated with chills and sweating, with recurrences every 2 to 3 weeks. She also reports left flank and abdominal pain, with some associated distention. She feels full easily during meals and often wakes up from sleep due to pain. There is no pedal edema, breathlessness, decreased urination, or facial puffiness. She feels easily fatigued and is described as getting more "white" by the parents. Her family and developmental histories are normal. Details of previous evaluation and care are not available.

On examination, she appears pale, quiet, and lethargic. Her pulse is 118 beats/min, her blood pressure 94/60 mm Hg, her respiratory rate is 22 beats/min, and her temperature is 101.2°F (38.4°C). Her weight and height are less than the third percentile. Diffuse hyperpigmentation is noted. There is no cyanosis, lymphadenopathy, clubbing, edema, or icterus. Abdominal examination reveals an increased girth of 46.5 cm, prominent veins, a firm liver edge 4.5 cm below the right costal margin with a liver span of 11 cm, and a massive spleen span of 11.5 cm. Results of the cardiovascular, respiratory, and central nervous system examinations are normal.

She has normal liver enzyme levels and a normal coagulation profile. Her renal function test results and electrolyte levels are normal. Her serum total protein level is elevated at 9.70 g/dL (97 g/L) (reference range, 6–8 g/dL [60–80 g/L]), and her globulin levels are elevated at 7.00 g/dL (reference range, 2.0–3.5 g/dL). The sedimentation rate is elevated at 60 mm/hour. The hemoglobin level is low at 7.1 g/dL (71 g/L) with a mean corpuscular volume of 75.1 μm^3 (75.1 fL). The white blood cell count is normal at 8,000/μL (8.0 × 10^9/L), but she is neutropenic, with an absolute neutrophil count of 800/μL (0.80 × 10^9/L). Her platelet count is normal at 143 × 10^3/μL (143 × 10^9/L). A reticulocyte count is 7.55%. A blood culture revealed no growth. Immunoglobulin (Ig) levels included IgA, 131 mg/dL (1,310 mg/L) (reference range, 27–195 mg/dL [270–1,950 mg/L]); IgG, 5,265 mg/dL (52.65 g/L) (reference range, 504–1,464 mg/dL [5.04–14.64 g/L]); and IgM, 458 mg/dL (4,580 mg/L) (reference range, 24–210 mg/dL [240–2,100 mg/L]). Human immunodeficiency virus (HIV) antibody and hepatitis B surface antigen levels were normal/negative.

Ultrasonography of the abdomen revealed hepatomegaly and splenomegaly, with multiple hypoechoic lesions diffusely involving the splenic parenchyma. Computed tomography of the abdomen and pelvis showed similar findings of splenomegaly, with a small, wedge-shaped, peripheral subcapsular hypodense area in the upper pole consistent with a splenic infarct. The splenic vein was dilated in caliber (1.1 cm) and tortuous. Hepatomegaly of 11.0 cm with normal attenuation was also noted. An additional test revealed the diagnosis.

THE DEFINITIVE DIAGNOSIS

A bone marrow aspirate revealed normal erythropoiesis, myelopoiesis, megakaryopoiesis, and maturation of cells lines and an M:E ratio of 3.5:1. A careful microscopic examination of the bone marrow specimen revealed *Leishmania donovani* (LD) bodies present extracellularly and intracellularly in macrophages (Fig).

The Disease

Leishmaniasis is a vector-borne disease occurring in tropical regions where there is a high prevalence of poverty in the community. The disease can occur in multiple forms, with cutaneous involvement being the milder form, and mucosal or visceral (kala-azar) forms associated with substantial morbidity and mortality. The causative agent, *L donovani,* exists in 2 forms: the flagellate promastigote in the sand fly vector and an aflagellate amastigote form in the human host. The promastigote is secreted into blood during a blood meal by the vector. The amastigote form exists in the phagolysosomes of the macrophages, resisting the acidic intracellular environment and multiplying within and causing cell death. These infected macrophages help the organism evade the immune system. *L donovani* and *Leishmania mexicana* predominantly cause visceral leishmaniasis. Rodent reservoirs maintain the zoonotic transmission, and human infection occurs when human activities bring them in contact with the reservoir and the vector. Among parasitic diseases, mortality from leishmaniasis ranks just behind that of malaria and schistosomiasis in children younger than 15 years.

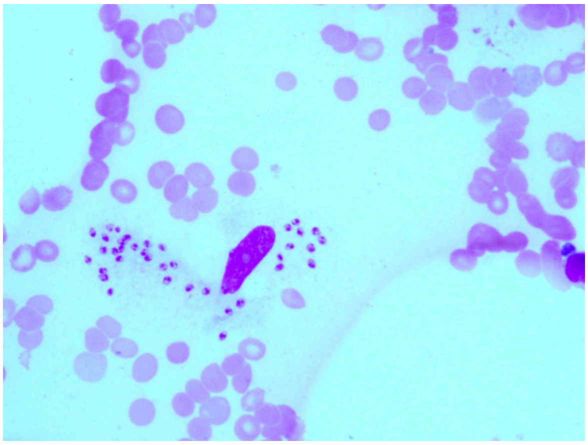

Figure. Giemsa stain showing intracellular LD bodies in the macrophages of the bone marrow aspirate (original magnification ×50).

The pathological hallmark of visceral leishmaniasis is hyperplasia of the reticuloendothelial system with abundant amastigotes in the histiocytes and Kupffer cells. Splenic infarcts, fatty infiltration of the liver, and erythrophagocystosis are late complications.

Visceral leishmaniasis typically affects children younger than 5 years (Table). A transient flulike illness with few symptoms is seen in many children after the sand fly bite. The illness in this situation is self-resolving. In 25% of children, classical kala-azar then sets in with an incubation period varying from months to years. High-grade fever, marked splenomegaly and hepatomegaly, hyperpigmentation, and severe cachexia develop over 6 months after the onset of illness. Skin hyperpigmentation in patients with visceral leishmaniasis is probably due to elevated cortisol levels. Patients with visceral leishmaniasis have a high level of inflammatory markers. Stimulation of the hypothalamic-pituitary-adrenal axis due to elevated cytokines and a consequent increase in corticotropin is thought to be responsible for increased cortisol levels causing stimulation of melanocytes and hyperpigmentation. (1) Untreated, it may eventually lead to severe pancytopenia, edema, ascites, and death due to secondary bacterial infections. Leishmaniasis is also an opportunistic infection associated with HIV. Laboratory tests usually reveal severe anemia, thrombocytopenia, and leukopenia, with elevated transaminase levels and hyperglobulinemia, usually IgG. Serologic testing in visceral leishmaniasis is used as a diagnostic tool due to higher levels of antileishmanial antibodies compared with other forms of the disease. Definitive diagnosis is by demonstration of amastigotes in tissue specimens or by the culture of the organism. Amastigotes can be identified by their appearance in Giemsa-stained specimens as small eosinophilic bodies known as LD bodies (Table). Bone marrow aspirate and biopsy are commonly used for diagnosis. In difficult cases, splenic aspiration can be performed, although it carries a high risk of life-threatening bleeding. (2)(3)(4)

The Centers for Disease Control and Prevention (CDC) in the United States provides multiple resources to help

TABLE. **Leishmaniasis: A Summary**

LEISHMANIASIS – THE DISEASE	NOTES
Clinical manifestations and laboratory characteristics	Classical visceral leishmaniasis is marked by high-grade fever, marked splenomegaly and hepatomegaly, hyperpigmentation, and severe cachexia. Severe disease is marked by pancytopenia, edema, ascites, and death. Laboratory parameters reveal severe anemia, thrombocytopenia, and leukopenia, with elevated transaminase levels and hyperglobulinemia.
Diagnosis	Tissue specimens—such as from skin sores (for cutaneous leishmaniasis) or from bone marrow (for visceral leishmaniasis)—are examined for the parasite for the presence of macrophages containing multiple amastigotes.
Treatment	Treatment with sodium stibogluconate or conventional/liposomal amphotericin B are recommended for therapy.

with the diagnosis of leishmaniasis. These services include examination of slides, culture mediums, in vitro culture, and polymerase chain reaction for the species identification of *Leishmania*. Serologic testing with rK39 rapid test for detecting antibodies against *Leishmania* is also among the services offered. The culture tubes are mailed by the CDC with shipping labels so that clinicians can obtain specimens and send them to the CDC for laboratory/pathology evaluation/testing. (5)

Differential Diagnosis

The common differential diagnoses include malaria, typhoid, miliary tuberculosis, infectious mononucleosis, lymphoma, and leukemia. In a patient with prolonged fever, weakness, cachexia, marked splenomegaly, hepatomegaly, cytopenias, and hypergammaglobulinemia who has had potential sand fly exposure in an endemic area, visceral leishmaniasis should be suspected after the other obvious disorders have been ruled out. (6)

Management

Management of visceral leishmaniasis requires therapy with either pentavalent antimonial compounds such as sodium stibogluconate, 20 mg/kg per day intravenously or intramuscularly for 28 days, or liposomal amphotericin B, 3 mg/kg per day intravenously on days 1 through 5 and 3 mg/kg per day on days 14 and 21 (Table). Recurrence of infection is not uncommon in the immunocompromised patient. Prevention of recurrences is by personal protection in endemic areas, vector control, and elimination of reservoirs. Currently, there are no vaccines available for visceral leishmaniasis. (7)

Patient Course

The patient was treated with liposomal amphotericin B, 3 mg/kg given for the first 5 days and on days 14 and 21. One month after therapy, at follow-up, she was afebrile, had gained 2 kg, and her pallor had resolved. Her liver and spleen were just 1.5 cm and 2.5 cm below the costal margins, respectively. The complete blood cell count was normal. However, the dark hue of her skin persisted.

Lessons for the Clinician

- Visceral leishmaniasis should be suspected in children hailing from endemic areas with prolonged fever, cachexia, and hepatosplenomegaly.
- Hyperpigmentation and hyperimmunoglobulinemia may be clinical and biochemical pointers toward the definitive diagnosis.
- The Centers for Disease Control and Prevention provides various resources for diagnosis by culture or serologic testing.

References for this article are at http://pedsinreview.aappublications.org/content/40/3/145.

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Case 3: Hepatosplenomegaly with Hyperpigmentation in a 6-year-old Girl

Suneel Mundkur, Sowmya Shashidhara, Shrikiran Hebbar and Shravan Kanaparthi

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4 Acute Onset of Fever, Jaundice, and Hyponatremia in a 17-year-old Boy

Kelly Kovaric, MD,* Coburn H. Allen, MD†

*Department of Pediatrics, St. David's Children's Hospital, Austin, TX
†Department of Pediatric Infectious Disease, Dell Children's Medical Center of Central Texas, Austin, TX

AUTHOR DISCLOSURE Drs Kovaric and Allen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old previously healthy boy presents with scleral icterus for 1 day. For approximately 10 days previously, he has had fever, arthralgias, and headache. He additionally complains of eye pain with movement, stiff neck, excessive thirst (drinking 64 oz of water a day), back pain, and nausea.

He denies rash, sore throat, cough, and congestion. He has not traveled anywhere. He has been taking approximately 8 g of acetaminophen daily for the past 2 weeks for joint pain.

On physical examination the patient's vital signs are normal except for fever (to 101.7°F [38.7°C]). He has scleral icterus, no periorbital swelling or edema, no meningismus, no hepatomegaly or splenomegaly, no swelling of the joints, and insect bites on his ankles but no rash.

Laboratory evaluation reveals the following values: sodium, 126 mEq/L (126 mmol/L); white blood cell count, 14,600/µL (14.6×10^9/L), with 75.5% neutrophils and 22% lymphocytes; hemoglobin, 12.6 g/dL (126 g/L); platelet count, $79{,}000 \times 10^3$/µL ($79{,}000 \times 10^9$/L); acetaminophen level, less than 2 µg/mL (<13.23 µmol/L); total bilirubin, 8.9 mg/dL (152.2 µmol/L); direct bilirubin, 5.8 mg/dL (99.2 µmol/L); lipase, 1,278 U/L (21.3 µkat/L); aspartate aminotransferase, 252 U/L (4.2 µkat/L); alanine aminotransferase, 241 U/L (4.0 µkat/L); alkaline phosphatase, 267 U/L (4.5 µkat/L); albumin, 2.7 g/dL (27 g/L); prothrombin time, 13.5 s; partial thromboplastin time, 33.9 s; blood urea nitrogen, 14 mg/dL (5 mmol/L); and creatinine, 1.0 mg/dL (88.4 µmol/L). Urine specific gravity is 1.006.

Poison control is consulted for chronic supratherapeutic acetaminophen ingestion and recommends acetylcysteine therapy. Liver enzyme levels decrease only slightly on acetylcysteine, and a fourth bag of acetylcysteine is started.

Additional history and laboratory examination reveal the diagnosis.

DISCUSSION

The adolescent's persistent fevers and the lack of improvement in his transaminase levels despite treatment with acetylcysteine prompted an infectious disease consultation. On further history, the patient revealed that the insect bites on his ankles were flea bites. Rodents had been seen in the home. In addition, the patient had cats and a dog that slept in his bed.

The patient was started on doxycycline, with resolution of symptoms within a day. A week later, his rickettsial panel returned with a typhus IgM titer of 1:1,024 and a typhus IgG titer of 1:1,024.

The Condition

Endemic or murine typhus usually presents with a triad of fever, headache, and rash. The rash is a nonpruritic macular or maculopapular rash starting on the trunk and spreading peripherally, sparing the palms and soles. However, in half the cases, rash is not present. (1)(2) Other clinical manifestations include arthralgias, pain with eye movement, cough, abdominal pain, confusion, and stiff neck. In 10% of patients, organ-specific complications arise (pneumonitis, hepatitis, meningoencephalitis, and renal failure); 2% to 4% of cases are considered severe, with shock, respiratory distress, multiple organ failure, hemorrhagic diathesis, consumptive coagulopathy, and severe neurologic compromise. (3)

Endemic typhus is caused by *Rickettsia typhi*, a gram-negative intracellular bacteria. Fleas spread *R typhi* from reservoirs (typically rodents) to humans via flea feces. Most commonly, flea feces are inoculated into the flea bite site, but flea feces can also be inhaled.

Endemic typhus should be distinguished from epidemic typhus. Epidemic typhus is spread by the human body louse and is caused by *Rickettsia prowazekii*. Epidemic typhus is more common in conditions of overcrowding and poor hygiene, such as in prisons and refugee camps.

Worldwide, endemic typhus is usually found in temperate climates and coastal areas in Asia, Australia, Mexico, and Spain. In the United States, endemic typhus can be found in southern Texas and California. This patient resided in central Texas, where there has been an increase in typhus cases since 2008. In 2008, after 13 cases of murine typhus were reported within 5 months, an investigation was conducted. The investigators found evidence of emergence of a suburban life cycle of endemic typhus involving cats, dogs, raccoons, and opossums and their fleas (in contrast to the urban life cycle, which is composed of rats and fleas). (4)

Diagnosis

The gold standard for diagnosis is indirect immunofluorescent antibody assay. (3) However, treatment should not be delayed while awaiting results. Additional laboratory abnormalities may include elevated aminotransferase levels, leukopenia, and thrombocytopenia. Some patients may have evidence of pneumonitis on chest radiography. Hyponatremia is most commonly attributed to increased vascular permeability due to endothelial cell injury by *Rickettsia typhi,* resulting in low intravascular volume and concentrated urine. Interestingly, our patient continued to have excessive thirst after admission, drinking 2,500 mL over 24 hours on the inpatient unit (even while receiving maintenance intravenous fluids with normal saline) and had dilute urine (urine specific gravity of 1.006) without evidence of renal injury (blood urea nitrogen level, 14 mg/dL [5 mmol/L]; creatinine level, 1.0 mg/dL [88.4 μmol/L]). He was persistently hyponatremic until we changed his diet to nil per os and continued his maintenance fluids with normal saline. To our knowledge, there is no pathophysiologic explanation of our patient's excessive thirst.

Of note, when considering rickettsial disease, a rickettsial panel is preferred because there is cross-reactivity between Rocky Mountain spotted fever (RMSF) and *R typhi* antibodies. (Both IgG and IgM are cross-reactive, but, per the Centers for Disease Control and Prevention [CDC], IgG antibodies are more accurate than IgM.)

In our patient's case, acute titers, taken 2 weeks after onset of symptoms, showed a typhus IgG titer of 1:1,024 as well as an RMSF IgG titer of 1:64. Convalescent titers showed typhus IgG 1:512 and RMSF IgG 1:256. Acute and convalescent titers were performed at 2 different laboratories so that a direct comparison between acute and convalescent titer numbers is difficult. The Texas Department of Health and Human Services classified this case as "probable typhus" because typhus IgG titers were higher than RMSF and the typhus IgG titer was 1:1,024 in the typhus-endemic area of Travis County. (2)(5)

Treatment

Doxycycline is the antibiotic of choice and has been shown to shorten the duration of illness. According to the *Red Book,* doxycycline should be given regardless of age. (6) Rapid resolution of symptoms, as in our patient, helps to confirm the diagnosis before serologic results are available.

Prevention

Prevention measures include treating domestic dogs and cats for fleas, preventing exposures to stray animals, placing screens on the windows, and eliminating food sources for animals by securing trash cans and pet food and throwing away fallen food. (7)

Lessons for the Clinician

- Although typhus is characterized by a triad of fever, rash, and headache, rash is absent in half of the patients.
- Consider rickettsial diseases in the differential diagnosis of patients with fever, arthralgias, headache, rash,

hyponatremia, thrombocytopenia, leukopenia, and organ dysfunction or inflammation.

- Begin therapy in suspicious cases immediately; do not await serologic results.
- Typhus can be found in suburban areas of Texas and California, with common reservoirs being cats, dogs, raccoons, and opossums.
- Send a rickettsial panel because there is cross-reactivity between Rocky Mountain spotted fever and *Rickettsia typhi* antibodies.

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in Brief

Malaria

Anuradha Rajagopalan, MD,* Christelle M. Ilboudo, MD†
**Child Health, South Providence General Pediatrics, and †Pediatric Infectious Diseases, University of Missouri Healthcare, Columbia, MO*

AUTHOR DISCLOSURE Drs Rajagopalan and Ilboudo have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

"With tears and toiling breath, I find thy cunning seeds, O million-murdering Death," wrote Sir Ronald Ross after his discovery in 1897 that the malaria parasite was transmitted by the *Anopheles* mosquito. Today, more than a century later, malaria continues to cause disease in millions of people worldwide. In 2015 alone, there were approximately 429,000 deaths due to malaria. Most of these deaths occur in sub-Saharan Africa in children younger than 5 years. Malaria is endemic in Africa, Latin America, Asia, parts of the Caribbean, Eastern Europe, and the South Pacific. Although global mortality and morbidity are improving, the number of cases in travelers is increasing. Per GeoSentinel Global Surveillance data, falciparum malaria is the most common serious febrile illness in returning travelers and the main cause of death. There were 1,724 cases of malaria imported to the United States in 2014. Most of these imported cases occur in people visiting friends and relatives in endemic areas of Africa and Asia. Of the 1,715 patients with imported malaria whose ages were known, 265 (15.5%) were children younger than 18 years.

Malaria is caused by protozoa of the genus *Plasmodium*. The 4 species infecting humans consistently are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*. Human infections from the simian parasite *Plasmodium knowlesi* are intermittently reported from Southeast Asia. Transmission of all species occurs through the bite of an infective female *Anopheles*. Other less common modes of transmission are through blood transfusion, organ transplant, needle sharing, and vertical transmission from mother to fetus.

Initial malaria symptoms can be nonspecific, with headaches, abdominal discomfort, fatigue, and myalgia. This is followed by fever, chills, perspiration, anorexia, vomiting, and worsening malaise. Young children can present with lethargy, poor feeding, and cough. The clinical picture in an immunologically naive traveler differs from that of a patient living in a malaria-endemic area, who has partial immunity. Relative immunity to malaria develops in areas of intense malarial transmission with repeated exposure to different strains of malarial antigen. This inhibits parasite multiplication and results in asymptomatic parasitemia (premunition). Immunity wanes over time with lack of exposure to the malarial antigen. People who have previously lived in endemic areas and are visiting friends and relatives often do not take chemoprophylaxis because they consider themselves immune. They are, therefore, at high risk for disease. In nonimmune travelers who have never been exposed to malaria, the incubation period is short, with most travelers developing symptoms of falciparum malaria within a month of leaving the endemic area. Clinical symptoms are severe and can progress rapidly, making it a medical emergency.

Rapid diagnosis and treatment is critical because full recovery is possible. Once progression occurs to severe malaria, most cases are fatal if left untreated. Severe

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malaria is characterized by 1 or more of the following; coma, metabolic acidosis, severe anemia, hypoglycemia, acute renal failure, or acute pulmonary edema.

The gold standard for laboratory diagnosis is light microscopy. Both a thick and a thin smear are examined for the parasite. The thick smear is a more sensitive tool for detection of the parasite, whereas the thin smear enables species identification and parasite count. The accuracy of detection depends on the skill of the microscopist. A skilled technician can detect parasites at densities of less than 10/μL of blood. A negative smear should be followed by 2 more smears at 6- to 12-hour intervals. A rapid diagnostic test, which detects parasite-specific antigen by immunochromatography, can be considered if a skilled technician is not available. The limitations of this test are that it cannot be used for species identification or parasite count. It cannot be used to distinguish new infections from recently treated ones because the rapid diagnostic test for *P falciparum* HRP2 remains positive for 1 to 5 weeks after therapy. Polymerase chain reactions are highly sensitive and useful for detecting mixed infections at low parasite densities, but results can take as long as 10 days and are performed only in reference laboratories. They can be used to study drug resistance and are generally reserved for special circumstances, such as treatment failure.

Certain genetic factors, such as the sickle cell trait, provide relative protection against *P falciparum*. Hence, sickle cell trait is more frequent in people of African ancestry than in other population groups. Similarly, hemoglobin C, the thalassemias, and glucose-6-phosphate dehydrogenase deficiency are more prevalent in malaria-endemic areas. Red blood cells negative for the Duffy blood group are resistant to infection by *P vivax*. Most Africans are Duffy negative, and, therefore, *P vivax* is rare in sub-Saharan Africa.

It is important to consider malaria in any traveler with a febrile illness who has returned from a malaria-endemic area in the past year, regardless of chemoprophylaxis history. In most cases surveyed, travelers with imported malaria had not adhered to a chemoprophylaxis regimen that was appropriate for the region of travel per the Centers for Disease Control and Prevention (CDC) recommendations.

Treatment is based on the infecting *Plasmodium* species, the clinical status of the patient, and the drug susceptibility of the infecting parasite. Children younger than 8 years diagnosed as having uncomplicated chloroquine-resistant *P falciparum* in the United States are treated with atovaquone-proguanil or artemether-lumefantrine as first-line agents. Quinine sulphate combinations with doxycycline and tetracycline, which are the next option, are not preferred in this age group. Quinine may not be available in capsule form, making dosing difficult. The pediatric dosage should be adjusted by weight and should never exceed the recommended adult dosage.

Children younger than 8 years with chloroquine-resistant *P vivax* are treated with mefloquine as first-line. In cases of *P vivax* and *P ovale* infections, primaquine is necessary for preventing relapses. Glucose-6-phosphate dehydrogenase screening is required before primaquine therapy. Severe malaria is treated in the United States with parenteral quinidine combined with doxycycline, tetracycline, or clindamycin as combination therapy. Intravenous artesunate therapy is preferred. This treatment is provided in an intensive care setting with continuous cardiac monitoring.

It is essential for health care providers to familiarize themselves with prevention strategies because millions of US residents travel each year to malaria-endemic regions. Prevention measures available are mosquito avoidance and chemoprophylaxis. There is no current vaccine for travelers. However, there are phase 3 trials investigating RTS,S/AS01, an injectable 4-dose vaccine series that offers partial protection against *P falciparum* in children aged 5 to 17 months. It was piloted in 2018 in sub-Saharan Africa.

Addressing malaria prevention in travelers is a balance between ensuring that all people at risk for infection are protected adequately while preventing rare adverse effects associated with these interventions. Chemoprophylaxis is the most effective method of preventing infection. Education about the risk of disease and evaluating for potential adverse effects by starting chemoprophylaxis 3 to 4 weeks before travel can help improve compliance. Malaria, although a deadly disease, is both preventable and curable. Clinicians need to maintain a high index of suspicion for this disease in febrile travelers returning from a malaria-endemic area.

COMMENT: Having worked in Liberia and Uganda, treatment of malaria was a common occurrence and was often done on an outpatient basis. But in my practice in the United States, cases have included children whose families traveled abroad either to their countries of origin or for vacations. It is critical for primary care providers to know how and when to prescribe chemoprophylaxis, and I have found the CDC travel website, https://wwwnc.cdc.gov/travel, incredibly informative. Choices in chemoprophylaxis will vary based on the age of the patient, potential adverse effects, and individual patient choices of frequency of doses and duration of treatment. It is critical to review these issues and find the optimal individualized chemoprophylaxis for families because adherence is key to prevention. As noted in this *In Brief,* more than 80% of travelers who became infected with malaria did not adhere to their recommended chemoprophylaxis. Appropriate testing for malaria is key to diagnosis, so asking about a travel history in any patient presenting with fever is essential. Once the diagnosis is made or highly suspected, accessing infectious disease consultants is important to ensure implementation of high-quality and best-care practices.

– Janet Serwint, MD
Associate Editor, *In Brief*

Malaria

Anuradha Rajagopalan and Christelle M. Ilboudo

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Urinary Tract Stones

Caren E. Gellin, MD*
**Department of Pediatrics, University of Rochester, Rochester, NY*

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A urinary tract stone, or urolithiasis, is defined as a formation of a stone in the kidney, bladder, or urethra. The epidemiology, imaging modalities, and treatment options for urolithiasis in pediatric patients has significantly evolved in the past several years. Although still more common in adults, the incidence of urolithiasis in children has increased by 6% to 10% annually during the past 20 years, with a current incidence of 36 to 57 per 100,000 US children. The reasons for this change remain unclear, but some hypotheses correlate the increase with obesity and dietary changes. However, current evidence has not confirmed these suspicions. Unlike the male predominance in adults, a strong overall sex preference does not exist in children except that males are more likely to be affected in the first decade of life and females are more likely to be affected in the second decade. Similar to adult stone composition, calcium oxalate and calcium phosphate are the most common stones, composing approximately 75% of cases of pediatric urolithiasis. Other types of stones include struvite, cystine, and uric acid stones. Another important difference between children and adults, which affects diagnostic evaluation and treatment, is that 80% of children have at least 1 risk factor for developing stones, such as abnormal urinary metabolism, a urinary tract infection (UTI), or a structural abnormality. Approximately 50% of children have a metabolic etiology resulting from decreased crystal-forming inhibitors or solute excess from decreased urine volume and/or increased solute excretion. In contrast, risk factors in adults are largely affected by patient dietary habits and comorbidities such as hypertension, diabetes, and obesity.

The clinical presentation of urolithiasis varies with age. Adolescents may have a more classic presentation of abdominal or flank pain, renal colic, and hematuria. Other symptoms can be less specific and include nausea, vomiting, dysuria, and urgency. In contrast, younger children are less likely to have typical renal colic symptoms, and 20% of children have an incidental finding of urolithiasis, which is important because it still may be associated with recurrence. In addition to exploring presenting symptoms, important historical features include the medical history, dietary patterns with special attention to fluid and sodium intake, medications and supplements, and family history. The vital signs of temperature and blood pressure are particularly important because fever can suggest a UTI, which may be associated with urolithiasis, and hypertension would suggest an alternate diagnosis, such as glomerulonephritis, especially if combined with edema. Poor growth can suggest an underlying metabolic cause and a risk factor for urolithiasis. On abdominal examination, tenderness can occur from the flank area to the lower quadrants depending on stone location, and costovertebral tenderness may be associated with obstruction. Laboratory evaluation on acute presentation should include a urinalysis and microscopy looking for hematuria, pyuria, or crystals, which, if present, are helpful in determining stone composition. A urine culture will diagnose a UTI that could prompt consideration of

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complications such as urolithiasis if it does not respond to standard antibiotic treatment. Finally, a creatinine level assesses renal function.

Diagnosing urolithiasis involves visualizing a stone on imaging or recovering a passed stone in the urine. A noncontrast spiral computed tomographic (CT) scan is the most sensitive imaging modality for identifying stones; however, the concerns over the morbidity of ionizing radiation and its cumulative effect, especially in children, is an important consideration. Therefore, the recommendation is to use ultrasonography as first-line imaging, which still boasts a sensitivity of approximately 70% and is an excellent means of identifying obstruction. If CT is needed for diagnosis or treatment planning, reduced-dose techniques are preferred if available. Abdominal radiography is limited because it detects only radiopaque stones and cannot identify obstruction, but it may be helpful if used in conjunction with ultrasonography. Although MRI may be considered as an alternative, it is not very accurate in detecting stones.

The first decision in the treatment of urolithiasis is to identify patients who require immediate stone removal to alleviate obstruction, prevent renal insufficiency, and/or control symptoms. Indications include UTIs causing obstruction, persistent severe pain despite pain management, and the anatomical variant of solitary kidney. The mainstays of treatment are aggressive hydration, pain control, antibiotics if a concomitant infection, and stone passage. Nonsteroidal anti-inflammatory drugs and opioids are the primary analgesics used, and spontaneous stone passage is possible with more distally located and smaller stones (<5 mm). In the recent American Urological Association/Endourological Society Guideline, observation with or without medical expulsion therapy (MET) with α-blockers is recommended for stones less than or equal to 10 mm in children. MET with α-blockers and calcium channel blockers leading to smooth muscle relaxation in the ureters has been a helpful adjunct in adults. In children, the few studies conducted have evaluated only α-blockers and indicate that treatment is safe, with significantly increased stone passage.

Failure of stone passage after intravenous hydration with or without MET is often due to anatomical abnormalities or stone composition (ie, struvite staghorn stones). At this point, consultation with a urologist is warranted. For smaller stones that do not pass and are less than or equal to 20 mm, ureteroscopy (URS) or extracorporeal shock wave lithotripsy (ESWL) are first-line surgical options. Urologists choose between the options depending on stone location, stone composition, comparative benefit-risk ratio, procedure-related instrument availability, and urologic expertise. Although not routinely recommended, some favor pre-stenting before URS to aid in ureteral dilation. For stones that are greater than 20 mm, the American Urological Association/Endourological Society recommends percutaneous nephrostolithotomy (PCNL) or ESWL with stent placement based on expert opinion; however, PCNL has led to higher stone-free rates than ESWL in a variety of studies in children. Equipment and techniques for pediatric patients undergoing PCNL continue to evolve to improve success and minimize risks. Of note regarding radiation exposure, CT is important for PCNL planning, and fluoroscopy is often used during both URS and PCNL, although using ultrasonography instead has been done in some institutions.

Because recurrence of urolithiasis ranges from 30% to 66% in children, addressing risk factors is a vital part of treatment. When a child's acute presentation has resolved, including being infection-free with normal eating, drinking, and activity, a further metabolic cause should be pursued. Stone analysis is particularly helpful and can lead to a more targeted approach. Otherwise, serum tests should include creatinine, bicarbonate, calcium, magnesium, phosphorus, and uric acid, with further tests depending on abnormalities. A 24-hour urine collection to identify urinary solute excretion best identifies urine abnormalities. If there is difficulty in obtaining the sample, a spot urine solute–creatinine ratio is a reasonable initial test. For many of the solute levels in both a 24-hour collection and a spot urine sample, normal values vary based on age and sex. Regardless of the stone composition, increased fluid intake is a main preventive measure. Dietary changes and pharmacologic therapy are possible prevention strategies that are highly dependent on the type of urinary tract stone.

In summary, while urolithiasis is not a common pediatric condition, the incidence has steadily increased over the past 2 decades for unclear reasons. The varied clinical presentation, particularly in young children, requires a high index of suspicion. Ultrasound is the preferred initial imaging modality for its reasonable sensitivity and lack of ionizing radiation. Treatment of stones is still evolving, with more centers using MET and newer equipment and techniques for surgical interventions. As a component of management, children with urolithiasis should undergo a comprehensive evaluation to identify risk factors in guiding recurrence prevention.

COMMENT: The US economic burden in pediatric patients for treatment of urinary tract stones is approximately 375 million dollars from hospitalizations and emergency department care. Generalist primary care providers and hospitalists need to be familiar with both the diagnosis and initial treatment of urinary stones. Medications that are important to inquire about because they have been associated with increased rates of stone formation include supplements such as vitamin C, vitamin D, and calcium and some diuretics, seizure medications, antibiotics, and corticosteroids. Patients on the ketogenic diet have also been noted to have a higher risk of urinary stone formation. The reasons for admission of patients include inability to take adequate oral fluids, need for intravenous analgesia, and significant risk factors, such as infectious etiology or sepsis, the patient has a transplanted or single kidney, and signs of renal obstruction, which require urgent intervention.

General pediatricians will want to partner with specialists if a patient does not pass the stone in a timely manner or requires surgical interventions. Patients at high risk for stone recurrence would benefit from a stone clinic with an interdisciplinary team that includes representatives from nephrology, urology, nutrition, and nursing. Younger patients who present with a urinary stone have a higher likelihood of recurrence because they have a higher likelihood of having an etiology from a metabolic, genetic, or anatomical cause, along with a longer life expectancy and lifetime exposure rates.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

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Urinary Tract Stones

Caren E. Gellin

Pediatrics in Review 2019;40;154
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Visual Diagnosis

An Infant with Rash and Hypercalcemia

Monica L. Arango, MD,* Avni N. Shah, MD†

*Department of Pediatrics and †Department of Pediatric Endocrinology, McGovern Medical School at UT Health, Houston, TX

PRESENTATION

A 3-week-old full-term breastfed infant boy presents with a 6-day history of vomiting, poor feeding, and lethargy. He was born via spontaneous vaginal delivery to a 33-year-old gravida 1 para 1 mother after an uncomplicated pregnancy. The delivery was complicated by meconium aspiration, with Apgar scores of 2 and 6 at 1 and 5 minutes, respectively. He developed intractable seizures and underwent therapeutic hypothermia as treatment for neonatal encephalopathy. He was discharged on day 12 after birth.

At presentation, his physical examination is remarkable for extensive, nonpigmented, nontender subcutaneous nodules palpable over the posterior surfaces of the arms and upper and lower back (Fig). Laboratory evaluation confirms the diagnosis.

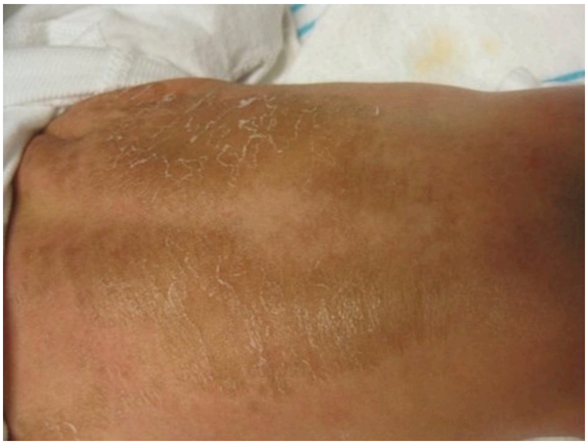

Figure. Infant with subcutaneous fat necrosis on upper back.

DIAGNOSIS

Laboratory evaluation reveals the following levels: serum calcium, 21.2 mg/dL (5.3 mmol/L); ionized calcium, 2.61 mg/dL (0.65 mmol/L); phosphorus, 4.9 mg/dL (1.58 mmol/L); magnesium, 1.7 mg/dL (0.69 mmol/L); albumin, 3.4 g/dL (34 g/L); alkaline phosphate, 115 U/L (1.92 μkat/L); intact parathyroid hormone, less than 5.5 pg/mL (<5.5 ng/L), 25-hydroxyvitamin D, 36 ng/mL (89.86 nmol/mL); 1,25-dihydroxyvitamin D, 104 pg/mL (270.4 pmol/L); and triglycerides, 230 mg/dL (2.6 mmol/L). The infant has hypercalcemia due to subcutaneous fat necrosis (SFN).

AUTHOR DISCLOSURE Drs Arango and Shah have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Review of his NICU course revealed a calcium level of 10.9 mg/dL (2.73 mmol/L) on day 8; the calcium level was 12.3 mg/dL (3.08 mmol/L) when corrected for hypoalbuminemia. The calcium level in the mother's milk is 29.2 mg/dL (7.30 mmol/L) (reference range, 30–35 mg/dL [7.50–8.75 mmol/L]), and maternal studies for hyperparathyroidism are normal. Retroperitoneal ultrasonography suggests early nephrocalcinosis, and the predisposition index for nephrocalcinosis (urinary calcium/creatinine ratio) is 20 (reference range, <2).

DISCUSSION

Calcium is regulated by the parathyroid gland. Low calcium level provides feedback to the gland to produce parathyroid hormone (PTH). PTH promotes calcium reabsorption in the kidney and activates 1-α-hydroxylase, which converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, leading to increased calcium absorption from the intestine. PTH also stimulates osteoclasts to release calcium from the bone. (1)

Severe hypercalcemia (calcium level, >12 mg/dL [>3 mmol/L]) is a life-threatening condition at any age, especially in newborns, with a mortality rate up to 15% in SFN. (2) It can be associated with kidney injury, with or without nephrocalcinosis, as well as cardiac complications such as arrhythmias and ST-segment elevation. (1)

Several causes of hypercalcemia in the perinatal period have been described, including primary hyperparathyroidism, hypervitaminosis D, maternal hyperparathyroidism in breastfeeding mothers, and, less commonly, genetic defects and SFN. (3) Hypothermia has been documented as a risk factor for SFN, and more cases have been reported since therapeutic hypothermia protocols have been established for the management of neonatal encephalopathy. (4)(5)

SFN is an uncommon granulomatous disorder that has been associated with perinatal asphyxia, trauma, or prolonged exposure to cooling therapies. It presents with dermatologic changes consisting of subcutaneous indurated nodular areas of purple color. These lesions are most commonly localized to the face, posterior trunk, chest, and proximal extremities; they may be followed by electrolyte disturbances, mainly hypercalcemia, in severe cases. (6)(7) To date, there is not a standard protocol for serial calcium monitoring or treatment of this condition in high-risk patients.

The mechanism of the hypercalcemia in SFN is not well understood. Akin et al (6) propose that it may be due to granulomatous cell infiltration of the damaged fat tissue causing necrosis and increased production of 1,25-dihydroxyvitamin D by macrophages in the area. The increased 1,25-dihydroxyvitamin D leads to increased calcium absorption from the gastrointestinal tract. (2)(6)(8)(9) Other possible explanations include increased osteoclast activation by prostaglandins and calcium release from necrotic fat cells. (6)(10)

Treatment of hypercalcemia includes aggressive fluid resuscitation to treat volume depletion and furosemide to inhibit renal reabsorption of calcium. Glucocorticoids may inhibit calcium absorption from the gastrointestinal tract and decrease 1-α-hydroxylase conversion of 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D. (1) Limited data suggest that there may also be a role for treatment bisphosphonates. Several case reports have documented a rapid decrease in calcium levels with this therapy. (11)(12)(13)(14) In the largest case series to date of infants with severe hypercalcemia due to SFN, 7 patients with similar characteristics were analyzed. Calcium levels were as high as 20.4 mg/dL (5.1 mmol/L), and the only patient who received pamidronate had a rapid, and permanent, resolution of otherwise refractory hypercalcemia. (3)

Pamidronate is a bisphosphonate that inhibits the activity of osteoclasts and bone turnover for weeks after its administration. (15)(16) It is not labeled for use in the pediatric population but has been widely used off-label in bone fragility disorders in children. Its adverse effects can include hypocalcemia and growth arrest. According to the literature, a single dose of pamidronate at 0.25 to 1.0 mg/kg has been found to be rapidly effective and well-tolerated. (3)(12)(17)

Long-term management of SFN includes a low-calcium, vitamin D–free formula, and serial calcium levels until nodules resolve, which could take 6 to 12 months. We suggest monitoring serum calcium levels every 1 to 2 weeks for 6 months to detect hypercalcemia in infants with signs of SFN. (15)

PATIENT COURSE

The infant was initially managed with fluid resuscitation and a continuous furosemide drip. He received 2 doses of prednisone (2 mg/kg per day) and a single dose of pamidronate intravenously (0.34 mg/kg) and had a rapid decrease in calcium levels over the next 12 to 24 hours. The hypertriglyceridemia is thought to be due to the mobilization of fatty acids from the adipose tissue and from elevations in very low-density lipoprotein. (14) After treatment, the calcium level was 9.7 mg/dL (2.42 mmol/L) and the ionized calcium level was 1.23 mg/dL (0.31 mmol/L). His triglyceride level peaked at 273 mg/dL (3.08 mmol/L) on postnatal day 28. He went home on a low-calcium, vitamin D–free formula and a phosphorus supplementation, which were both discontinued after the nodules resolved at 2 months of age. His elevated triglyceride levels normalized by 4 months of age.

Summary

- Infants exposed to therapeutic hypothermia are at risk for subcutaneous fat necrosis, which can be complicated by hypercalcemia.
- Serum calcium levels should be followed every 1 to 2 weeks for 6 months to detect hypercalcemia in all infants with signs of subcutaneous fat necrosis.
- In patients who develop severe hypercalcemia, with or without nephrocalcinosis, early therapy with pamidronate should be considered to prevent further kidney injury or cardiac complications.

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Visual Diagnosis

Annular Lesions in a 3-month-old Girl

Joseph S. Tadros, MD,* Yang Yu, MD,[†] Anne W. Lucky, MD[†‡]

*University of Cincinnati College of Medicine, Cincinnati, OH
[†]Department of Dermatology, University of Cincinnati Medical Center, Cincinnati, OH
[‡]Division of General and Community Pediatrics, Cincinnati Children's Hospital, Cincinnati, OH

PRESENTATION

A previously healthy, full-term, 3-month-old girl presents with several annular erythematous patches and plaques on the head, scalp, and upper body. The lesions first appeared at 6 weeks of age and progressively spread to involve the face and upper trunk. Past treatments included the topical antifungal butenafine 1% cream twice daily for 3 weeks without substantial improvement. The rash does not worsen with sun exposure, and there are no pets in the household. The mother notes that the patient's 2 older siblings both presented with similar eruptions as infants. The patient's older sister experienced several scaly erythematous lesions on her scalp at 4 months of age that cleared by 6 months after treatment with oral griseofulvin. Her older brother also presented with a similar spot on the abdomen in his first year of life that cleared after butenafine treatment. The family history is notable only for hypothyroidism in the mother and maternal aunt.

The initial physical examination revealed several well-defined, 1.5- to 3-cm, annular, erythematous patches and plaques, some of which exhibited peripheral scale. The lesions were found on the scalp, forehead, neck, upper chest, and right arm (Figs 1 and 2). Telangiectasias were noted around the periphery of several lesions. A potassium hydroxide (KOH) examination of the peripheral scale was negative for fungal elements. Electrocardiography and cardiac examination findings were normal. Additional laboratory evaluation identified the diagnosis.

DIAGNOSIS

Neonatal lupus erythematosus (NLE) was suspected, and laboratory evaluation revealed an unremarkable complete blood cell count with a normal differential cell count and a negative antinuclear antibody but was positive for anti-Ro/SSA (98.3 U) and anti-La/SSB (111.7 U) autoantibodies. Based on the clinical and laboratory findings as well as the family history of similar lesions in 2 previous siblings that resolved within their first year after birth, a diagnosis of NLE was made.

DISCUSSION

NLE is a rare acquired autoimmune disease caused by the placental passage of immunoglobulin G antibodies against Ro/SSA, La/SSB, or U1-RNP from the mother to the neonate after the first 16 weeks of pregnancy. The incidence is estimated to be 1 in 20,000 births. The most common clinical manifestations of

AUTHOR DISCLOSURE Drs Tadros, Yu, and Lucky have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

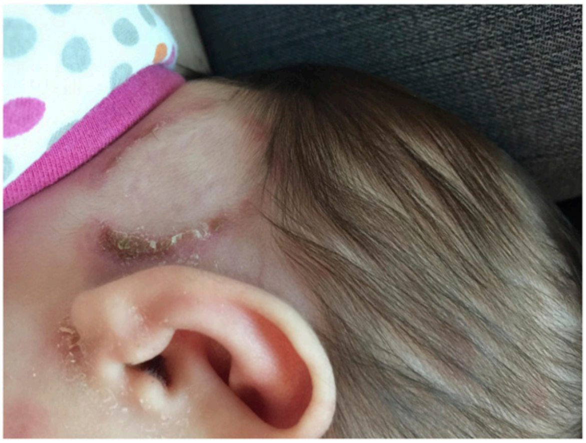

Figure 1. Annular plaque with an erythematous border and yellow crust noted behind the ear.

NLE include skin lesions and congenital heart block with or without concurrent endocardial fibroelastosis or dilated cardiomyopathy. Other findings may include hemolytic anemia, thrombocytopenia, neutropenia, hepatitis with hyperbilirubinemia, and subependymal pseudocysts with hemorrhage.

Cutaneous lesions in NLE consist of annular, erythematous, sometimes scaly patches and plaques most commonly on the central regions of the face (classic periorbital pattern) and occasionally on the scalp, neck, and arms, as in our case. The patches can also be atrophic, with overlying telangiectasia. Other skin presentations include urticaria, ulcerated plaques, targetoid lesions, persistent telangiectasias, or small papulonodules. Cutaneous NLE typically presents in the first months after birth and may be present at birth; an analysis from a national registry demonstrated median onset at 6 weeks. Diagnosis of NLE is made by identification of the characteristic lesions in the first year after birth and detection of antibodies against Ro/SSA, La/SSB, or U1-RNP in the child or mother. Histologic findings show a mononuclear infiltration with vacuolization of the basal layer, which is nonspecific. Skin biopsy is usually unnecessary and should be performed only when the diagnosis is unclear via clinical and laboratory analysis.

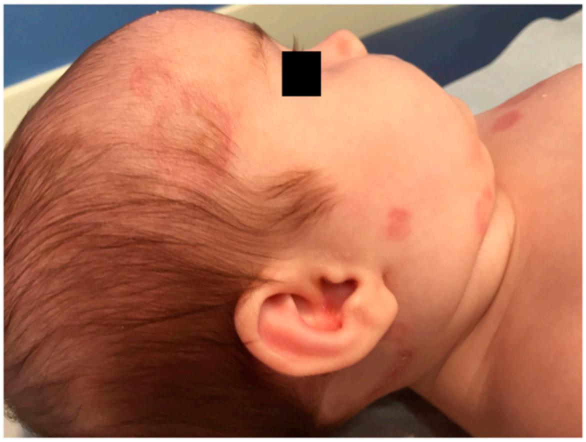

Figure 2. Multiple erythematous, annular plaques, some with scale and crust, on the scalp, jawline, and neck.

The most serious and well-known complication of NLE is heart failure secondary to congenital conduction block, which develops in utero between 18 and 24 weeks' gestation. Anti-La/SSB antibodies have been implicated in its pathogenesis, but the mechanism is still unclear. Approximately 15% to 30% of children with NLE are born with congenital heart block. Studies estimate that the mortality rate is between 20% and 30% in those with cardiac involvement; the rate is higher in those with simultaneous cardiomyopathy. Nearly 60% of children affected by congenital heart block, specifically, third-degree atrioventricular blocks, require placement of a pacemaker. Neonates with first- or second-degree blocks may remain asymptomatic until adulthood or experience spontaneous resolution.

Differential Diagnosis

Few conditions present with lesions similar to those of NLE (Table). However, it is not uncommon for NLE to be mistaken for tinea corporis because of the annular lesions. As in our case, patients are often treated with topical antifungal agents.

Management: Child and Mother

Children with NLE should avoid sunlight because exposure can precipitate flares. Sunscreen of sun protection factor 30 or higher should be applied before any UV light exposure. Low-potency topical corticosteroids may be used for skin lesions. Laser therapy is an option if there are residual telangiectasias after lesions have regressed. Systemic corticosteroids, intravenous immunoglobulin, and other immunosuppressive agents may be used for severe hepatic and hematologic complications; these agents are not indicated for isolated cutaneous findings.

Patients with cardiac involvement require serial electrocardiography to assess for a prolonged PR interval and sustained bradycardia because there is a low threshold for placement of a pacemaker to avert the risk of heart failure. It is important that these children receive further follow-up to check for the development of some autoimmune diseases, particularly juvenile idiopathic arthritis. Retrospective studies have noted that some patients with NLE eventually developed mixed connective tissue disease, psoriasis, or Hashimoto thyroiditis. Without considering family history, it is not entirely clear whether children with NLE have an increased risk of systemic lupus erythematosus (SLE).

TABLE. Common Differential Diagnoses of Neonatal Lupus Erythematosus

CONDITION	CLINICAL FEATURES
Tinea corporis	Rarely diagnosed in neonates. Lesions follow a centrifugal morphology and are typically inflammatory with fine scale. Usually there is contact with an infected family member or pet.
Erythema annulare centrifugum	May affect any age group and has rarely been reported in neonates. It is characterized by arcuate lesions, sometimes large (up to 10 cm) originating on the trunk and extremities with trailing scale.
Annular erythema of infancy	Presents within the first couple of months as progressively enlarging, erythematous, nonscaly plaques. Lesions may be distributed on the face, trunk, and extremities.
Erythema gyratum atrophicans transiens neonatale	Presents within the first couple of days after birth as arcuate erythematous patches with raised borders and central atrophy.
Early congenital syphilis	Presents within the first 3 months after birth. The rash is characterized by macular, bronze-colored lesions on the palms and soles and papules with scattered petechiae around the nose and mouth. Vesiculobullous eruptions may also be seen.
Cutis marmorata telangiectatica congenita	Presents within the first days after birth as blue-violaceous, reticulated lesions that appear more erythematous in cold environments and do not disappear with warmth. Lesions tend to be on the lower extremities, but they may affect the upper extremities and trunk. Eight case reports have been described as "like NLE."

Nearly 50% of mothers are asymptomatic for any autoimmune disease after having their first child with NLE. However, there is a risk of developing autoimmune diseases, most notably Sjogren syndrome or SLE. Thus, evaluation and continued follow-up is recommended. Mothers who have had children born with congenital heart block should be aware that the risk of recurrence in a subsequent pregnancy is 15%. Routine ultrasonography and electrocardiography should be performed in women who have had a previous child with NLE or who have an existing autoimmune disease with high anti-La/SSB antibody titers.

Prognosis

The prognosis of NLE depends on the organ system involved. Patients with isolated cutaneous findings have an excellent prognosis because lesions tend to resolve over 4 to 6 months, corresponding with the clearance of maternal immunoglobulin G antibodies from the child's circulation. However, residual scar formation, dyspigmentation, and persistent telangiectasias may occur. Complete heart block can be fatal. All patients must be screened for heart block, and this should be monitored in subsequent pregnancies. Hepatic and hematologic abnormalities in patients with NLE usually resolve in 4 to 6 months. In rare instances, cholestatic hepatitis may progress to liver failure, which portends a poor prognosis.

Patient Course

Approximately 2 months after presentation, the skin lesions had almost all resolved without treatment. Electrocardiography and laboratory evaluation were negative for other systemic involvement. Her mother was advised to be evaluated for SLE. Judicious monitoring of the siblings by a pediatrician for cardiac arrhythmias was also recommended.

Summary

- Neonatal lupus erythematosus (NLE) is a rare autoimmune disease that most commonly presents with skin and cardiac manifestations.
- The most common lesions in NLE consist of erythematous annular patches and plaques on the scalp, face, and neck. It is commonly misdiagnosed as tinea corporis; thus, physicians must keep NLE in the differential diagnosis, especially if there are hepatic or hematologic abnormalities present or if there is a family history of autoimmune disease.
- The skin lesions in NLE resolve spontaneously after 4 to 6 months; congenital heart block is the major source of long-term morbidity and mortality.
- Asymptomatic mothers at the time of presentation and children with NLE should continue routine follow-up given the small risk of developing systemic autoimmune diseases.

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Cough

Ajay S. Kasi, MD,* Rory J. Kamerman-Kretzmer, MD[†]

*Division of Pediatric Pulmonology, Department of Pediatrics, Emory University, Atlanta, GA
[†]Division of Pediatric Pulmonology and Sleep Medicine, Children's Hospital Los Angeles, Los Angeles, CA

Practice Gaps

Cough in children is a common chief complaint. It is important to adopt a systematic approach to the evaluation and management of chronic cough and avoid symptomatic treatment. The use of pediatric-specific cough management algorithms improves clinical outcomes.

Objectives

After completing this article, readers should be able to:

1. Distinguish between acute and chronic cough in children.
2. Identify cough characteristics and specific cough "pointers" requiring further evaluation.
3. Effectively begin management of nonspecific cough and suspected protracted bacterial bronchitis.
4. Identify children with cough who need evaluation by a specialist.

INTRODUCTION

Cough is a common reason for pediatric outpatient visits. Cough as a manifestation of respiratory disease can range from minor upper respiratory tract infections to serious conditions such as bronchiectasis. Acute cough in children is mostly caused by upper respiratory tract infections (URTIs). Chronic cough, defined as daily cough of at least 4 weeks in duration, (1) can be associated with an underlying serious disorder and, hence, requires systematic and thorough clinical evaluation. There is high-quality evidence that a systematic approach to the management of chronic cough in children using pediatric-specific cough algorithms improves clinical outcomes. (1) Treatment of cough should be based on the etiology. Because cough is a common presenting complaint, pediatricians must become familiar with the initial evaluation and management of children with cough to establish a diagnosis and determine appropriate therapy.

EPIDEMIOLOGY

Cough is one of the most common complaints presented at physician visits and accounts for an estimated 29.5 million annual outpatient visits. (2) The prevalence of chronic cough in children is estimated to be 5% to 10%. (3) In the United States, approximately 2 billion dollars per year is spent on over-the-counter (OTC) cough

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ABBREVIATIONS

BAL	bronchoalveolar lavage
CT	computed tomography
GERD	gastroesophageal reflux disease
ICS	inhaled corticosteroid
OTC	over-the-counter
PBB	protracted bacterial bronchitis
PCD	primary ciliary dyskinesia
URTI	upper respiratory tract infection

products. Additional costs in the management of cough include physician visits, laboratory and radiologic tests, prescription medications, school absence, and parental leave. (4) Chronic cough in children is associated with parental stress, increased physician visits, and disrupted sleep. (5)

PATHOPHYSIOLOGY OF COUGH

Cough is an important airway-protective reflex that involves "a forceful expulsion of air from the lungs that is under both voluntary and involuntary control." (6)(7) Cough receptors are located in the epithelium of the pharynx, larynx, and tracheobronchial tree. Chemical irritants, mechanical stimuli, and inflammatory mediators stimulate cough receptors. When stimulated, afferent impulses are sent through the vagus nerve to the cough center in the brain stem and pons. The efferent limb includes the vagus, phrenic, and spinal motor nerves to the larynx, diaphragm, and other muscles of expiration.

Cough has three phases: 1) a deep inspiration, 2) closure of the glottis accompanied by relaxation of the diaphragm and contraction of the muscles of expiration, and 3) opening of the glottis. Intrathoracic pressure (up to 300 mm Hg in adults) can be generated during the second phase. Sudden opening of the glottis during the third phase of cough generates high air flow velocity, which helps clear airway debris. (6) In addition, cough improves mucociliary clearance in both healthy individuals and those with lung disease. (4)

An effective cough depends on intact receptors, as well as the afferent and efferent limbs of the cough pathway. Repeated stimulation of the cough receptors can lead to decreased sensitivity of the receptors. This can be seen in children with recurrent aspiration and gastroesophageal reflux (GERD). (6) Respiratory muscle weakness seen in neuromuscular diseases can also lead to inadequate cough, atelectasis, and pneumonia.

CLINICAL APPROACH

When evaluating children with respiratory symptoms, a detailed clinical history and thorough physical examination will guide diagnosis and management. Essential aspects in the history of a child presenting with cough include the nature of the cough, duration, aggravating and relieving factors, diurnal variation, and associated symptoms. Certain cough characteristics may point to the etiology of cough in children. A "brassy" or "barking" cough could suggest croup, tracheomalacia, or habit cough. "Paroxysmal" cough, especially with an inspiratory whoop, generally suggests *Bordetella pertussis* infection. It can also be caused by *Bordetella parapertussis*, adenovirus, parainfluenza, respiratory syncytial virus, and mycoplasma. (8) "Staccato" cough in infants suggests infection with chlamydia. "Honking" cough can be seen in psychogenic cough. Cough productive of airway casts suggests plastic bronchitis. Plastic bronchitis is a rare condition in which bronchial casts lead to airway obstruction and respiratory distress in children with cardiac and respiratory diseases. The pathogenesis of airway cast formation remains unclear, and it has been attributed to abnormal pulmonary lymphatic vessels and drainage in children with cardiac disease or lymphatic anomalies. (6)

Pediatric cough can be classified in several ways based on 1) duration of symptoms (acute or chronic), 2) cough character (dry or wet), and 3) likelihood of identifying an etiology for cough (specific or nonspecific).

Based on duration of symptoms, cough can be classified as acute or chronic (lasting >4 weeks). (9) Young children rarely expectorate sputum, so it is important to determine whether the cough is dry or wet. Characterizing the cough as dry or wet aids in following pediatric-specific cough algorithms for evaluation and management. Specific cough is associated with clinical features suggestive of an underlying etiology, whereas nonspecific cough is not associated with any identifiable respiratory disease or known etiology after a thorough clinical assessment. (8)(9)

A thorough physical examination should be performed in children with cough. Height and weight should be recorded to assess for failure to thrive. Inspection of the nose and throat may reveal signs of allergic rhinitis or postnasal drip. The ears should be examined because impacted wax or foreign bodies in the external auditory meatus can be associated with chronic cough in some children via stimulation of the Arnold nerve (a branch of vagus nerve) reflex. (6)(7) The chest wall should be inspected for any deformity. The chest should be auscultated to assess the nature, quality, and symmetry of air entry along with any abnormal breath sounds, such as wheezes or crackles. The fingers should be examined for the presence of clubbing. If the child coughs during the examination or is capable of coughing on request, the character of cough should be assessed, and the chest wall should be palpated for vibrations due to retained airway secretions. (7)(10) Neurologic examination with assessment of muscle tone can help identify children with neurologic impairment or neuromuscular disease who are at risk for developing aspiration lung disease.

ACUTE COUGH

Acute cough has been defined as cough of less than 2 weeks in duration. (8) Viral URTIs are the most common cause of acute cough in children. (10) However, children with acute cough should be assessed for signs and symptoms of a more serious pathologic condition, such as inhaled foreign body or lower respiratory tract infection. (8)(10) Lower respiratory tract infection should be suspected in children with acute cough, fever, tachypnea, or crackles. Acute cough can be the initial manifestation of a chronic respiratory disease. Hence, children with acute cough should be evaluated for failure to thrive, digital clubbing, or chest deformity suggesting an underlying chronic respiratory disease. (11) A typical history of aspirating a foreign body may not be evident in all cases, thus sudden onset of cough or dyspnea should prompt the clinician to consider foreign body aspiration. (10) A normal chest radiograph does not exclude foreign body aspiration; hence, bronchoscopy is indicated when there is a suspicion for an aspirated foreign body. (11)

Healthy children experience URTIs several times a year. (9)(10) Cough caused by URTI generally resolves within 1 to 3 weeks in children. A prospective cohort study of acute cough in preschool-aged children presenting to primary care showed that 50% of children had recovered in 10 days but that 10% of children were symptomatic with cough at 25 days. (12) In most children, acute cough caused by viral URTIs is self-limiting and requires only supportive treatment, such as antipyretics for fever (to comfort the child), and adequate intake of liquids. A recent Cochrane review reports no good evidence for the effectiveness of OTC medicines in acute cough. (13) Clinicians should counsel parents about the potential harm of using OTC cough medications in children. Antibiotics are not beneficial in acute cough due to viral URTIs, and bronchodilators confer no benefit in acute cough in children without asthma. (8)(11) Parents must be counseled about the natural history of cough due to URTIs and warning signs (eg, tachypnea, persistent fever, progressive cough) requiring further evaluation to avoid subsequent office visits for a subsiding cough. (11)

In recent years, there has been an increased interest in using honey for the treatment of acute cough in children. A Cochrane review evaluated the effectiveness of honey for acute cough in children and reported that honey may be better than no treatment, diphenhydramine, and placebo for the symptomatic relief of cough. The authors concluded that “there is no strong evidence for or against using honey.” (14) Clinicians should caution parents about the use of honey in infants due to the risk of botulism. (15)

Some indications for performing a chest radiograph in a child with acute cough are 1) uncertain diagnosis of lower respiratory tract infection in a child with persistent fever, tachypnea, or crackles; 2) suspected foreign body aspiration; and 3) an atypical clinical course with progressively worsening cough or hemoptysis. (11)

CHRONIC COUGH

In children 14 years and younger, “chronic cough is defined as the presence of daily cough for at least 4 weeks in duration.” (1)(9) This definition is based on the natural history of resolution of cough after URTI in children. Cough lasting for at least 4 weeks warrants careful assessment because it may suggest a serious underlying condition in which early diagnosis (eg, airway foreign body leading to bronchiectasis) would improve outcomes. (1)(9) There is high-quality evidence that using pediatric-specific chronic cough algorithms improves clinical outcomes in children. (1)(16)(17)(18) In evaluating children (age ≤14 years) with chronic cough, we encourage readers to refer to the American College of Chest Physicians’ evidence-based clinical practice guidelines (9) and the CHEST Guideline and Expert Panel Report on the use of management algorithms, (1) which guide the discussion herein. The evaluation of children with chronic cough should include a thorough history, physical examination, chest radiography, and, when age-appropriate, spirometry. Collectively, cough “pointers” are diagnostic clues that may identify an underlying etiology for a chronic cough (Table 1). The presence of these pointers classifies chronic cough as specific (likely to have an identifiable etiology) or nonspecific (unlikely to have an identifiable etiology) and guides evaluation and management.

SPECIFIC COUGH

In children with chronic cough, clinicians should assess for symptoms and signs that are suggestive of an underlying disease (whether respiratory or systemic), termed *specific cough pointers* (Table 1). Specific cough pointers suggest that cough is due to an underlying disorder, and further diagnostic evaluation is indicated, often in conjunction with a pediatric pulmonologist. (8)(9)(19) Some specific cough pointers include chest pain, dyspnea, digital clubbing, feeding problems, failure to thrive, and abnormal pulmonary auscultation. Diagnoses such as structural airway abnormalities, aspiration lung disease, bronchiectasis, and interstitial lung disease are associated with chronic specific cough (Table 2).

The cough characteristics should be elicited from parents because this may point to the etiology of cough. A wet or productive cough indicates the presence of excessive airway mucus. Even when sputum is present, young children rarely expectorate airway secretions. (20) Daily wet cough is a useful clinical marker in predicting a specific cause of

TABLE 1. **Specific Cough Pointers (1)(8)(9)**

HISTORY	EXAMINATION
Abnormal cough characteristics (eg, brassy, barking, staccato, paroxysmal cough)	Abnormal breath sounds
Cardiac abnormalities	Abnormal cardiac examination
Chest pain	Chest wall deformity
Cyanosis	Digital clubbing
Daily wet or productive cough	Failure to thrive
Dyspnea, including exertional dyspnea	Hypoxemia
Feeding problems	Tachypnea
Fever	**TESTS**
Foreign body aspiration	Abnormal chest radiograph
Hemoptysis	Abnormal spirometry
History of previous lung disease	
Immune deficiency	
Medication (angiotensin-converting enzyme inhibitors) or illicit drug use	
Neurodevelopmental problems	
Pertussis or tuberculosis exposure, or risk factors	
Recurrent pneumonia	

cough. (19) A daily wet cough can be seen in suppurative lung disease from a variety of etiologies, including cystic fibrosis, primary ciliary dyskinesia (PCD), or other causes of bronchiectasis.

Evaluation of chronic cough should include a discussion about the presence of dyspnea. If there is no report of dyspnea at rest, the parent/child should also be asked about exertional dyspnea. Exercise is a common trigger for cough and wheezing in children with hyperactive airways. (6) Although exertional dyspnea can be associated with asthma, it may also suggest airway or parenchymal lung disease requiring further evaluation. If there is associated chest pain, further details regarding the characteristics of the chest pain should be obtained. If the child has ever had hemoptysis, the clinician should evaluate for tuberculosis, an inhaled foreign body, suppurative lung disease, or vascular abnormalities. A history of cardiac abnormalities can be important, as congenital heart disease can be associated with structural airway abnormalities (eg, airway malacia) and anatomical compression. (21) Children with congenital heart disease can develop cough from congestive cardiac failure with pulmonary edema or from respiratory ciliary dysfunction due to underlying PCD. Expectoration of airway casts in a child with congenital heart disease suggests plastic bronchitis that requires evaluation by a pediatric cardiologist and pulmonologist. Recurrent pneumonia can be due to immunodeficiency, suppurative lung disease, congenital lung abnormalities, tracheoesophageal fistula, and other conditions. A detailed feeding history should be obtained in children with chronic cough. An episode of choking or acute onset of cough in a child should raise concern for an inhaled foreign body. Cough or choking during feeding should alert the physician to possible recurrent, small-volume pulmonary aspiration. The neurodevelopmental history should be reviewed because aspiration lung disease can be seen in children with developmental delays. In the birth history, prematurity and prolonged oxygen requirement suggest bronchopulmonary dysplasia, which can cause persistent respiratory symptoms in children. A diagnosis of PCD must be considered when there is a history of neonatal respiratory distress, tachypnea, or a supplemental oxygen requirement in a term infant. (22) Family history should be reviewed for asthma and other chronic respiratory conditions, such as cystic fibrosis or PCD. The social history should assess for environmental factors that can cause cough, such as tobacco smoke exposure, indoor pollutants,

TABLE 2. Causes of Cough in Children (6)(9)(11)

- Acute (<2 wk)
  - Upper and lower respiratory tract infections
    - Viruses
    - Mycoplasma
    - Other bacteria
  - Foreign body aspiration
- Chronic (≥4 wk)
  - Pulmonary causes[a]
    - Asthma
    - Bronchiectasis, chronic suppurative lung disease
    - Cystic fibrosis
    - Eosinophilic lung disease
    - Foreign body aspiration
    - Illicit drugs
    - Immunodeficiency (with recurrent infection)
    - Interstitial lung disease
    - Irritative/noninfective bronchitis (eg, smoke, pollution)
    - Pertussis
    - Primary ciliary dyskinesia
    - Protracted bacterial bronchitis
    - Recurrent aspiration (laryngeal cleft, tracheoesophageal fistula, swallowing dysfunction)
    - Structural airway abnormalities
    - Tuberculosis and other chronic infections
  - Extrapulmonary causes
    - Cardiac disease
    - Habit cough
    - Gastroesophageal reflux (controversial)
    - Mediastinal mass
    - Medications (eg, angiotensin-converting enzyme inhibitors)
    - Otogenic cough

[a] *This is not a comprehensive list because almost any airway or parenchymal lung disease can cause chronic cough.*

or allergens. The medication history should be reviewed because children taking angiotensin-converting enzyme inhibitors can develop chronic cough as an adverse effect. Tuberculosis is a common cause of chronic cough in children from countries where tuberculosis is endemic. Hence, the history should include recent travel or immigration from endemic countries, exposure to individuals with tuberculosis, and other risk factors. Failure to thrive or digital clubbing in a child with chronic cough can be due to cystic fibrosis or other chronic pulmonary diseases. Abnormal auscultatory findings such as wheezing or crackles suggest specific causes of cough. Wheezing may indicate asthma or intrathoracic airway lesions (eg, tracheomalacia), and crackles can be heard in suppurative lung disease or interstitial lung disease. Monophonic wheezing can be auscultated in large airway obstruction from an aspirated foreign body, airway malacia, or compression (eg, enlarged lymph node).

Even if the child is fully immunized, pertussis should be suspected in a child with spasmodic cough, with posttussive emesis, or when there has been contact with an individual with pertussis infection. The appropriate diagnostic test in a child with suspected pertussis depends on the child's age and duration of symptoms. (1) Readers are referred to the American Academy of Pediatrics' *Red Book* for additional guidance regarding testing and management of pertussis. (23)

Although cough can be a symptom of asthma, most children with isolated cough do not have asthma. (9) Children with asthma generally have recurrent (and variable) symptoms, airflow obstruction with bronchial hyperresponsiveness, and airway inflammation. Readers are referred to the National Heart, Lung, and Blood Institute guidelines for the diagnosis and management of asthma. (24)

Children with specific cough pointers require further evaluation, often in conjunction with a pediatric pulmonologist. Children with chronic wet cough should be promptly evaluated, and early consultation with a pediatric pulmonologist should be considered. (19) Evaluations conducted by pediatric pulmonologists in children with chronic wet cough to identify the etiology often include chest imaging, comprehensive pulmonary function tests, bronchoscopy, sweat chloride testing for cystic fibrosis, a videofluoroscopic swallow study, a ciliary biopsy with electron microscopy (for PCD), and immunologic function tests. (9) In summary, the diagnostic evaluation of chronic specific cough is guided by the clinical findings identified from the specific cough pointers (Table 1). The particulars of these evaluations are not discussed in this review.

NONSPECIFIC COUGH

Nonspecific cough is chronic cough in the absence of specific cough pointers, with normal findings on spirometry (if age-appropriate) and chest radiography. Nonspecific

TABLE 3. **Approach to Chronic Cough in Children 14 Years and Younger (1)(9)**

1. Is cough present daily for ≥4 weeks?
2. A. Thorough history and physical examination, particularly focusing on:
- Cough characteristics (eg, brassy, barking, staccato, paroxysmal cough)
- Specific cough pointers (Table 1)
- Effect of cough on the child and the family
2. B. Spirometry (for patients aged >3–6 y) and chest radiography
3. If specific cough pointers are present, proceed with appropriate evaluation (eg, pertussis testing when suspected) or referral to a pediatric pulmonologist
4. Nonspecific cough with normal spirometry (when feasible) and normal chest radiograph:
- Evaluate exposures (eg, smoke, pollutants) and intervene (eg, tobacco cessation)
- Watchful waiting for 2 weeks
- If persistent, consider an empirical trial of therapy based on presumed diagnosis (eg, inhaled corticosteroids for dry cough or antibiotics for suspected protracted bacterial bronchitis)
- Follow up in 2–4 weeks to assess response, discontinue therapy to confirm/refute presumed diagnosis, and refer to a pediatric pulmonologist if persistent/recurrent

cough is typically a dry cough for which no underlying etiology is identifiable after a thorough assessment. In most children, nonspecific cough is due to a viral respiratory infection (postviral cough) that resolves spontaneously with time and is not due to a serious etiology. (9) Some children can have a slow recovery of the airway epithelial mucosal cells and hypersensitivity of the cough receptors after a respiratory infection causing prolonged cough. (7)

For most children with nonspecific cough, the initial recommended step is a period of watchful waiting for 1 to 2 weeks (Table 3). The parents can be reassured, and the child can be reevaluated in 2 weeks. At follow-up, the child must be assessed for persistent cough and evaluated for emergence of any specific cough pointers. (9)

If cough persists at follow-up, clinicians can discuss the options with parents: 1) continued watchful waiting and reassessment in 2 weeks or 2) a trial of therapy. If the parents opt for watchful waiting, children must be evaluated in the subsequent 2 weeks for resolution of cough, and a trial of therapy should be considered if cough persists. At this point, it is important to distinguish between nonspecific dry cough and wet cough.

For nonspecific dry cough, asthma can be a cause, particularly if the child has other atopic features (eczema, allergic rhinitis) and a family history of asthma. Some children with asthma can have cough as the predominant symptom. (7) However, unless wheezing and dyspnea are also present, few children with isolated nonspecific cough have asthma. (10) An empirical trial of a bronchodilator (short-acting β_2 agonist) and a low-dose inhaled corticosteroid (ICS) can be administered when asthma is suspected. (1)(9) It can be difficult to exclude asthma as a cause of chronic dry cough in young children who are unable to perform reliable spirometry, and it may be challenging to identify exertional dyspnea and chest discomfort in young children. A randomized, placebo-controlled trial of inhaled albuterol and ICSs in children with isolated cough showed no benefit of these therapies compared with placebo. (25) Therefore, it is important that trials of asthma therapy are effectively administered (using a spacer with a metered-dose inhaler), are given over a predefined time frame (2–4 weeks), and have concrete therapy end points. (9)(11) If an empirical trial of therapy is pursued, the child should be reassessed in 2 to 4 weeks. If the cough does not improve with a daily low-dose ICS in 2 to 4 weeks, the dose should not be increased, and the medication should be stopped. At follow-up, if cough resolved with an empirical trial of asthma therapies, this can suggest underlying asthma or spontaneous resolution of cough (the period effect). Hence, to confirm the diagnosis, a trial off the medication should be performed. If cough recurs, the asthma therapies should be resumed. At each follow-up visit, the clinician should review specific cough pointers, as well as evaluate tobacco smoke exposure, other pollutant exposure, parental expectations, and evidence of any underlying illness. When the clinical diagnosis of asthma in young children is challenging, or if there is uncertainty in the diagnosis of asthma, consider evaluation by a pediatric pulmonologist. (10)

For nonspecific isolated wet cough, a diagnosis of protracted bacterial bronchitis (PBB) should be considered if there are no other symptoms and signs. PBB is a common cause of isolated chronic wet cough in children, and it is often misdiagnosed as asthma. (26) Bronchitis refers to inflammation of the bronchus or bronchi. (6) PBB-like conditions were reported in the past few decades; however, its existence was initially controversial. In the early 1980s, a single-center retrospective review of 20 children who underwent bronchoscopy and were diagnosed as having chronic bronchitis showed that these children had bronchoscopic features of airway inflammation, purulent airway secretions, mainly *Haemophilus influenzae* on bacterial culture, and most had clinical improvement after treatment with antibiotics. (27) In the early 2000s, a prospective cohort study of children with chronic cough showed that most of the children had wet cough, increased neutrophils in the bronchoalveolar lavage (BAL) fluid, and a positive BAL bacterial culture and that the cough resolved after treatment with antibiotics. In this study, PBB was the most common diagnosis for chronic cough in children. (28) PBB is recognized as a common cause of chronic wet cough in children and has been incorporated into several pediatric chronic cough management guidelines. (9)(11)(26)(29)(30)

PBB can be diagnosed clinically when all 3 of the following criteria are met: 1) the presence of chronic (>4 weeks) wet or productive cough, 2) the absence of specific cough pointers (ie, symptoms or signs that could suggest other causes of wet or productive cough), and 3) resolution of cough after a 2- to 4-week course of an appropriate oral antibiotic (usually amoxicillin-clavulanate). (26)(29) PBB can be seen in infants, young children, and adolescents. Children with PBB generally appear well, have normal growth, and do not have adventitious breath sounds, digital clubbing, or other signs of suppurative lung disease. Auscultation of the lungs may reveal a rattling sound suggestive of airway secretions. (20) The chest radiograph is normal or may show peribronchial changes, and spirometry (when feasible) is normal. (29) PBB is associated with a persistent bacterial infection and neutrophilic inflammation in the airways that leads to increased mucus production, airway inflammation, and chronic cough. PBB has been speculated as a potential prebronchiectasis state in some children with chronic wet cough. (20) If the child can expectorate, a sputum culture should be performed. If flexible bronchoscopy and BAL are performed, mucopurulent secretions are noted in the airways, and airway malacia (tracheobronchomalacia) can be seen. (29) Bacteria commonly identified from the BAL or sputum in children with PBB are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. There is high-quality evidence in children with chronic wet/productive cough (without specific cough pointers) that using appropriate oral antibiotics improves cough resolution. (30) PBB is treated with a prolonged (2-week) course of antibiotics, typically amoxicillin-clavulanate. Amoxicillin-clavulanate is widely used because it is effective against common pathogens identified in PBB. Other antibiotics, such as oral cephalosporins, trimethoprim-sulfamethoxazole, or macrolides, may be used. (29) If the wet cough persists despite 2 weeks of antibiotics, an additional 2 weeks of antibiotics can be prescribed to complete a total of 4 weeks of therapy. Biofilms produced by bacteria are speculated to be a reason for prolonged antibiotic courses in the treatment of PBB. (26) A study reported increased likelihood of bronchiectasis on chest computed tomographic (CT) scan in children with chronic wet cough that failed to resolve despite 4 weeks of oral antibiotic therapy. (31) Recurrent PBB has been suggested as a risk factor for developing chronic suppurative lung disease (clinical symptoms of bronchiectasis without CT findings of bronchiectasis) or bronchiectasis. (26) Therefore, if chronic wet cough fails to respond to or recurs despite 4 weeks of antibiotic therapy, clinicians should refer the child to a pediatric pulmonologist for evaluation.

Habit cough is characterized by loud, repetitive cough, often described as having a honking or barking quality. Habit cough can occur in both children and adolescents, can last from weeks to months, and is commonly misdiagnosed as asthma. (32) Cough is characteristically absent during sleep. (33) Physical examination findings are normal other than cough, and no organic cause is identified after investigations are performed. A preceding viral respiratory infection is often suggested as an inciting factor. (32) Before arriving at a diagnosis of habit cough, many children may have received medications such as bronchodilators, ICSs, antibiotics, montelukast, or reflux medicines. Tic disorders must be considered when children have vocal (cough tics) and motor tics. Suggestion therapy, generally using a distractor such as sipping warm water along with resisting the urge to cough, has been successful in treating habit cough. (32) Hypnosis has also been used to treat habit cough in children. Children with habit cough may need evaluation by a psychologist or psychiatrist if symptoms do not resolve with suggestion therapy. (34)

Gastroesophageal reflux disease is a common cause of chronic cough in adults; however, pediatric data have not established GERD to be the sole etiology of nonspecific chronic cough in children. (9) The relationship between GERD and cough is complex in children, as either can precipitate the other. (35) Because cough is common in children, and respiratory symptoms may exacerbate underlying GERD, it may be challenging to distinguish cause and effect in children. (9) Infants frequently regurgitate, yet cough is not a common association in healthy infants with these episodes. An empirical trial of reflux medications in children with nonspecific isolated chronic cough is not recommended unless children have other symptoms suggestive of reflux. (1)(11)

Upper airway cough syndrome and postnasal drip are common causes of chronic cough in adults but are controversial as causes of chronic nonspecific cough in children. (7)(9) There is insufficient evidence that postnasal drip, resulting from allergic rhinitis and sinusitis, is associated with chronic cough in children. Sinusitis has been associated with allergic rhinitis in children, but it is not associated with cough once existent atopy or allergic rhinitis are controlled. Children with allergic rhinitis can have a throat-clearing type of cough. In children with signs of allergic rhinitis, allergen avoidance and a trial of therapy (oral antihistamine or intranasal corticosteroids) is indicated. (11) Although atopy increases the likelihood of having asthma, it is neither sensitive nor specific for asthma. Hence, routine allergy testing is not indicated in the evaluation of children with nonspecific dry cough. (1) Current guidelines for pediatric chronic cough recommend against an empirical approach toward the treatment of upper airway cough syndrome in children with nonspecific isolated dry cough. (1)(11)

Exposure to environmental tobacco smoke causes adverse respiratory health outcomes and has been associated with increased coughing in children. Exposure to other pollutants, such as particulate matter and indoor biomass combustion, is also associated with increased coughing illnesses in children. (9)(11) Current pediatric chronic cough guidelines recommend that in all children with cough, tobacco smoke exposure should be evaluated, and families should be offered interventional options for the cessation of exposure. (9) Readers are encouraged to refer to the American Academy of Pediatrics' clinical practice policy to protect children from tobacco, nicotine, and tobacco smoke. (36)

INVESTIGATIONS

Spirometry (if age-appropriate) and chest radiography should be performed as initial evaluations in children with chronic cough. An abnormal chest radiograph suggests a specific cause of cough, but a normal chest radiograph does not exclude respiratory disease (eg, bronchiectasis). Findings on the chest radiograph may help guide further evaluations for chronic cough. Bilateral pulmonary hyperinflation is commonly seen in asthma but can also be seen in other chronic respiratory diseases. Unilateral hyperinflation or collapse of the lung can suggest an aspirated foreign body or intraluminal pathology that would require further imaging and bronchoscopy. A right-sided aortic arch may be a normal variant or can be associated with a vascular ring. (6) Organ laterality defects, such as situs inversus totalis, detected on routine imaging in a child with chronic oto-sino-pulmonary disease should prompt further evaluation for PCD. (22)

Spirometry is a useful clinical test to screen for lung function abnormalities in children with chronic cough. Pulmonary function tests are used to 1) assist in the diagnosis of lung disease by describing and quantifying the impairment in physiologic function, 2) monitor the course of respiratory disease in patients, and 3) assess response to therapy. Spirometry requires good patient effort and cooperation to provide reliable results. Most children can perform valid spirometry by age 6 years. In experienced pediatric pulmonary function laboratories, spirometry results can be obtained in children as young as 3 years. (37) Abnormalities in spirometry findings suggest a specific cause of cough, but normal spirometry results do not exclude respiratory disease. An obstructive pattern detected on spirometry implies asthma or other obstructive airway diseases. In children with obstructive airway disease, spirometry should be performed before and after administration of a bronchodilator. Improvement in airway obstruction after inhalation of a bronchodilator usually indicates a diagnosis of asthma. However, some children with asthma can have normal spirometry results. (1) For a detailed review of spirometry interpretation, readers are referred to a *Pediatrics in Review* article by Kaslovsky and Sadof. (38)

Additional tests to aid in the diagnosis of respiratory disease in a child with chronic cough depend on the history, physical examination findings, presence of specific cough pointers, and clinical suspicion of a particular etiology. Tests include chest CT scans, flexible bronchoscopy with BAL, ciliary biopsy with electron microscopy (for PCD), and genetic studies for cystic fibrosis and PCD. Most of these evaluations are undertaken by pediatric pulmonologists. Pediatric chronic cough management guidelines recommend against routinely performing additional tests such as allergy testing, bronchoscopy, and chest CT. These tests should be individualized and performed based on the child's clinical symptoms and signs. (1)

MEDICATIONS

Management of cough in children should be directed at identifying the etiology of cough and arriving at an accurate diagnosis. Treatment should be based on the underlying etiology and not targeted toward suppression of cough. There is no good evidence for the effectiveness of OTC cough medications in treating acute cough in children, and these medications can cause serious harm. For a review of OTC cough and cold medications, readers are referred to a *Pediatrics in Review* article by Lowry and Leeder. (39)

There is good evidence that in children with nonspecific chronic cough, an empirical approach targeted toward upper airway cough syndrome, GERD, or asthma should not be used unless there are other clinical features consistent with these diagnoses. (1) In some instances of nonspecific dry cough in young children, an empirical trial of inhaled bronchodilators and ICSs is used when asthma is suspected. As described previously, if an empirical trial of asthma medications is used, a definite period should be set (2–4 weeks), and the child should be reassessed for resolution of cough to confirm or refute the suspected diagnosis. If there is no response to asthma therapies, the medications should be stopped because asthma is unlikely. (11) If the cough did not respond to treatment with ICSs, children should not be treated with increased doses of ICSs. (9) Antibiotics are used when a diagnosis of PBB is suspected in a child with chronic nonspecific isolated wet cough. A systematic approach to the management of chronic cough by using pediatric cough management algorithms improves clinical outcomes. (1)(16)(18)

Summary

- Acute cough in children is usually caused by viral upper respiratory tract infections, which are self-limiting. There is no good evidence of effectiveness of over-the-counter cough medicines in acute cough, and they can cause serious harm in children. (13)
- Based on consensus, in children 14 years and younger, chronic cough is defined as the presence of daily cough for at least 4 weeks. (1)
- Strong evidence supports using a systematic approach, including a detailed history, thorough physical examination, and assessment of specific cough pointers, to guide the diagnosis, testing, and management of children with chronic cough. (1)
- Protracted bacterial bronchitis can be diagnosed in children with chronic wet cough without signs of an alternative cause who have resolution of cough after 2 to 4 weeks of treatment with an appropriate oral antibiotic. (30)
- In children with chronic cough, management must be based on the etiology of the cough. Based on strong research evidence, the use of pediatric-specific cough management algorithms improves clinical outcomes. (18)

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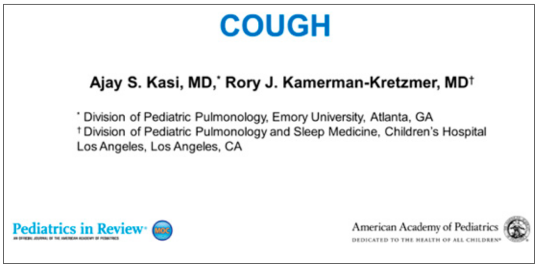

COUGH

Ajay S. Kasi, MD,* Rory J. Kamerman-Kretzmer, MD†

* Division of Pediatric Pulmonology, Emory University, Atlanta, GA
† Division of Pediatric Pulmonology and Sleep Medicine, Children's Hospital Los Angeles, Los Angeles, CA

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1. A 10-year-old girl with a medical history of asthma presents to the office for evaluation of a 5-week history of daily dry cough. She reports occasional bouts of shortness of breath, which improve with the use of her bronchodilator inhaler. She denies fever, nasal congestion, or chest pain. Which of the following factors support the classification of her cough as chronic?
   - A. Absence of fever and nasal congestion.
   - B. Characterization of cough.
   - C. Clinical response to the use of a short-acting β_2 agonist.
   - D. Presence of daily cough for greater than 4 weeks.
   - E. Previous diagnosis of asthma.
2. Children and adolescents with chronic cough with characteristics suggestive of specific underlying etiologies should be evaluated promptly and may benefit from a consultation with a pediatric pulmonologist. Which of the following clinical scenarios involving chronic wet cough would be most appropriate for a pediatric pulmonology referral?
   - A. Allergic rhinitis with postnasal drip.
   - B. Congenital heart disease with airway casts.
   - C. Gastroesophageal reflux disease with weight loss.
   - D. Moderate persistent asthma controlled with inhaled corticosteroids.
   - E. Tic disorder with vocal tics including habit cough.
3. A 9-year-old girl presents for an initial visit to establish care in your practice after recently moving to the United States. The mother states that she has always suffered from frequent respiratory infections, for which she has been prescribed multiple courses of antibiotics. She reports having wet cough with sputum production daily and shortness of breath with physical activity weekly. The mom is also concerned with her slow rate of growth and weight loss of 8 lb over the past year. On physical examination she is below the 5th percentile in both height and weight for her age. You note coarse crackles through the bilateral lung fields and mild digital clubbing. Based on the cough pointers in the history and findings on physical examination, which of the following is the most likely underlying diagnosis of this patient's chronic cough?
   - A. Cystic fibrosis.
   - B. Pertussis infection.
   - C. Retained foreign body.
   - D. Tracheoesophageal fistula.
   - E. Tuberculosis infection.
4. A 5-year-old previously healthy boy is brought to the pediatrician's office for evaluation of prolonged cough. The mother reports that the boy's illness began 4 weeks ago with fever of 3 days' duration, nasal congestion, and cough. The mother is concerned because the cough has persisted despite resolution of fever and improvement of other symptoms. The cough is described as dry and presents both during the day and at night. On physical examination the boy is well-appearing and in no distress. Chest auscultation reveals good air entry bilaterally and no wheezing or crackles. Findings on the chest radiograph are within normal limits. Which of the following is the best next step in management?
   - A. Initiate a trial of a short-acting inhaled β_2 agonist and inhaled corticosteroid.
   - B. Order pulmonary function tests.
   - C. Prescribe a 2-week course of amoxicillin-clavulanate.
   - D. Recommend supportive care and reassess the patient in 2 weeks.
   - E. Refer to a pulmonologist for flexible bronchoscopy.

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5. A 12-year-old previously healthy girl is brought to the clinic with a 5-week history of wet cough occasionally productive of yellow sputum. She denies fever, chest pain, dyspnea, or blood in the sputum. There is no history of cardiac or lung disease and no recent travel or exposures. A chest radiograph ordered 1 week earlier revealed mild peribronchial changes, and spirometry results were within normal limits. On physical examination today she is well-appearing and in no distress. Height and weight are at the 50th percentile. Chest examination reveals good air entry bilaterally with minimal rattling of airway secretions auscultated. There is no cyanosis or digital clubbing observed. Which of the following is the best next step in management?

   A. Initiate a short-acting inhaled β_2 agonist and an inhaled corticosteroid.
   B. Obtain a chest computed tomographic scan to rule out bronchiectasis.
   C. Order genetic testing for cystic fibrosis.
   D. Prescribe a 2-week course of amoxicillin-clavulanate.
   E. Refer to a pulmonologist for flexible bronchoscopy with bronchoalveolar lavage.

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Tuberculosis in Children

Peter J. Holmberg, MD,* Zelalem Temesgen, MD,[†] Ritu Banerjee, MD, PhD[‡]

*Division of Pediatric Hospital Medicine, Department of General Pediatric and Adolescent Medicine,
and [†]Division of Infectious Disease, Mayo Clinic, Rochester, MN
[‡]Division of Pediatric Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN

Practice Gaps

Although tuberculosis (TB) is an ancient disease, it continues to cause significant morbidity and mortality throughout the world, including among children. Knowledge of appropriate TB screening, diagnostic testing, and treatment recommendations is of vital importance for primary care providers when caring for children at high risk for TB.

Objectives

After completing this article, readers should be able to:

1. Understand the epidemiology of pediatric tuberculosis (TB).
2. Describe the mechanisms of TB acquisition and host response, including T-cell–mediated actions and granuloma formation.
3. Discuss the importance of comorbid conditions, specifically human immunodeficiency virus type 1, on the acquisition and progression of TB disease.
4. Identify risk factors for acquisition of TB infection.
5. Recognize the utility of tests for latent TB infection (LTBI), including the tuberculin skin test, interferon-γ release assays, and the effect of age and Bacille Calmette-Guérin vaccination status on interpretation of results.
6. Define the differences among TB, multidrug-resistant TB, and extensively drug-resistant TB.
7. Understand the principles of therapy and drug regimens for LTBI and TB disease (including drug-resistant TB).

INTRODUCTION

One of the most common infectious diseases worldwide, tuberculosis (TB) is estimated to affect almost 1 in 3 individuals across the globe. Despite relatively cheap and accurate diagnostic assays as well as established effective treatment regimens, TB remains a leading cause of death annually. When diagnosed and appropriately treated, TB mortality in children approaches zero. However, with an estimated yearly burden of 1 million new pediatric cases worldwide and most

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ABBREVIATIONS

BCG	Bacille Calmette-Guérin
CDC	Centers for Disease Control and Prevention
CXR	chest radiograph
DOT	directly observed therapy
EMB	ethambutol
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
IGRA	interferon-γ release assay
INH	isoniazid
LTBI	latent tuberculosis infection
Mtb	*Mycobacterium tuberculosis*
NTM	nontuberculous mycobacteria
RIF	rifampin
PZA	pyrazinamide
TB	tuberculosis
TST	tuberculin skin test

of these remaining undiagnosed, TB continues to pose a substantial threat to global child health. Furthermore, most pediatric infections in the United States occur in US-born individuals. All of these issues reveal the importance of pediatric providers being familiar with the epidemiology, natural history, clinical manifestations, diagnosis, and management of TB in children.

EPIDEMIOLOGY

Mycobacterium tuberculosis (Mtb), the pathogen that causes TB, infects up to one-third of the world's population. (1)(2) A chronic granulomatous infection, TB is a leading cause of death worldwide and results in greater mortality than any other single infectious organism, exceeding even human immunodeficiency virus (HIV). (2)(3) Despite drops in TB incidence and mortality over time, more than 2 billion people remain infected, and greater than 1 million individuals die yearly from TB, including approximately 200,000 children. (3) Primarily a disease of low- and middle-income countries, TB mortality is disproportionately concentrated in the youngest of children, with 80% of childhood TB deaths occurring in those younger than 5 years. (4) Historically, epidemiologic data on global mortality in children younger than 5 years have not included TB as a cause of death. (4)(5) However, recent modeling suggests that not only is TB the most common infectious cause of death in children younger than 5 years, but it is likely the sixth most common overall cause of death in young children. One of the most striking aspects of TB is that almost all (96%) of the deaths in children occur in those not receiving treatment for the infection. In fact, the mortality rate for children receiving appropriate therapy is less than 1%. (4) This is particularly worrisome given the fact that of the 1 million estimated new cases of TB yearly in children younger than 15 years, almost two-thirds are either undiagnosed or untreated. (6) In the United States, the overall number of TB cases increased in 2015 for the first time in 22 years, and this number included more than 1,000 newly documented infections in children. (7) These data highlight the importance of a pediatrician's familiarity with TB pathogenesis, symptoms, screening recommendations, and treatment.

TRANSMISSION AND PATHOGENESIS OF INFECTION

TB can cause infection almost anywhere in the body but is primarily a disease of the lower respiratory tract. (2) Initial infection with Mtb is considered a primary infection and in children is almost exclusively the result of exposure to an adult with TB disease. (8) Bacilli are spread by the expectoration and subsequent inhalation of Mtb-containing droplet nuclei that are small enough to pass into the lower respiratory tract. Larger droplets are generally excluded by the upper airway structures and bronchial epithelial cells. (9)(10) Childhood acquisition of Mtb is almost always from adults because young children generally have paucibacillary and noncavitary disease, along with an inadequate cough physiology to expectorate infectious sputum.

In immunocompetent persons, inhaled Mtb is bound to the surface of alveolar macrophages and is phagocytosed into a tight vacuole. The intracellular phagosome fuses with a lysosome, forming a phagolysosome complex. Within this, bactericidal elements, including reactive nitrogen and oxygen species, suppress and kill the mycobacterial pathogens, limiting Mtb growth. (9)(11) This initial response involves the innate immune system and, in most patients, is sufficient to clear the initial bacillary burden, effectively eliminating infection. (11)

In other individuals, innate immunity is inadequate to control the infection, and bacilli continue to multiply inside macrophages. By several mechanisms, including the arrest of phagolysosome fusion, Mtb actively work to survive this first stage of the host immune response. (1)(2) When replication of Mtb continues, bacilli spread to the interstitium of the lungs. Here, monocytic and dendritic immune cells transfer Mtb to regional lymph nodes, both activating adaptive immunity and providing a means of extrapulmonary spread. (1)(2)

In most cases, a T-cell–mediated host response ensues over the following weeks and promotes T- and B-cell activation and migration to the focus of infection. (12)(13) As various immune cells accumulate at the site, a granuloma composed of macrophages, lymphocytes, and dendritic and epithelioid cells is formed. (9)(10) This granuloma consists of a central area of infected and apoptotic macrophages enclosed by a layer of T and B cells. (14) Most commonly, the granuloma that forms is sufficient to control but not eliminate the bacillary load, which can persist in that environment for decades. (14)(15) This is considered a latent TB infection (LTBI) and is defined as the evidence of immune sensitization to Mtb without clinical signs or symptoms of disease. (16)

In a small number of individuals, the adaptive immune activity is inadequate to control infection, and Mtb continue to replicate unabated. When this happens, bacilli spread inside and outside of the lungs, resulting in the active form of TB known as *primary disease*. (2) In more than 90% of patients, this occurs within the first 12 months after exposure. (17) However, active disease at any point within 2 years of infection is considered primary TB. (1)(13) Not surprisingly, progression to primary disease occurs most frequently in infants. (1)(17) In fact, the risk of developing primary disease in infants is estimated to be 50%, including a 10% to 20% risk of disseminated disease or TB meningitis. For those aged 2 to 10 years, the risk of progression to active disease drops to less than 5%. A second peak in disease progression occurs in adolescence, when the risk of disease after primary infection increases to 10% to 20% (Table 1). (18)

Active TB includes a diverse spectrum of presentations and is perhaps better thought of as a continuum of disease instead of simply active TB. Individuals can be found anywhere along a spectrum from subclinical TB consisting of asymptomatic bacterial replication (1)(16) all the way to severe disease with septic shock, multiorgan failure, respiratory failure, and death. (19) Of the 3 initial outcomes of TB exposure (Fig), primary disease is by far the least common.

A second form of active TB is termed *reactivation disease*. After varying periods of latency, and generally in the setting of immune senescence or suppression, mycobacteria may begin to proliferate to the point that the granuloma can no longer control the microbial load. (2)(9)(10) Caseation necrosis occurs and granulomas eventually break down, allowing the release and spread of bacilli. Granulomatous decay into the distal bronchioles allows mycobacterial dissemination through expectoration. (15) The lifetime risk of reactivation has been estimated to be 5% to 10% in patients with LTBI. (9)(13)(20) Reactivation most often occurs in the first 2 to 5 years after primary infection and is generally not seen until late childhood and adolescence. (8)(20)(21) Of particular importance is the effect that HIV has on LTBI and the risk of reactivation.

HIV CO-INFECTION

HIV plays a major role in much of the disease burden seen in children in low- and middle-income countries, and those with HIV co-infection have a substantially higher case fatality rate than those without. (6)(22) No other factor has as large an effect on the progression of LTBI to active disease as HIV infection. (8) Indeed, individuals with HIV have a 20- to 40-fold greater risk of developing primary, active disease and a 50- to 110-fold greater risk of progressing from LTBI to active disease. (10) Initially, the reason behind the increased risk was thought to be due to the reduction in $CD4^+$ T-lymphocyte count. Although this does play a role, (2) it has more recently been shown that the risk of active TB increases in HIV-infected persons soon after acquiring HIV, when CD4 counts are normal, suggesting a role beyond simply total CD4 levels. (22) Other factors, including the recruitment and function of CD4 cells at sites of infection, are, therefore, important in TB and HIV co-infection, although more work is needed to clearly define these. (9)

RISK FACTORS FOR TB INFECTION IN CHILDREN

LTBI occurs when an individual has an immunologic test positive for infection with Mtb but is asymptomatic and has no abnormalities on physical examination or chest radiography (CXR). It is difficult to ascertain the number of children living with LTBI, although 1 study estimates that more than 7 million children acquire TB infection each year

TABLE 1. **Age-Related Risk of Evolution from Primary Infection to Primary Disease**

AGE AT PRIMARY INFECTION, Y	RISK OF PROGRESSION TO PULMONARY DISEASE, %	RISK OF PROGRESSION TO CENTRAL NERVOUS SYSTEM/MILIARY DISEASE, %
<1	30–40	10–20
1–2	10–20	2–5
>2–5	5	0.5
>5–10	2	<0.5
>10	10–20	<0.5

Adapted from Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. *2004;8(4):397. Reprinted with modifications with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union.*

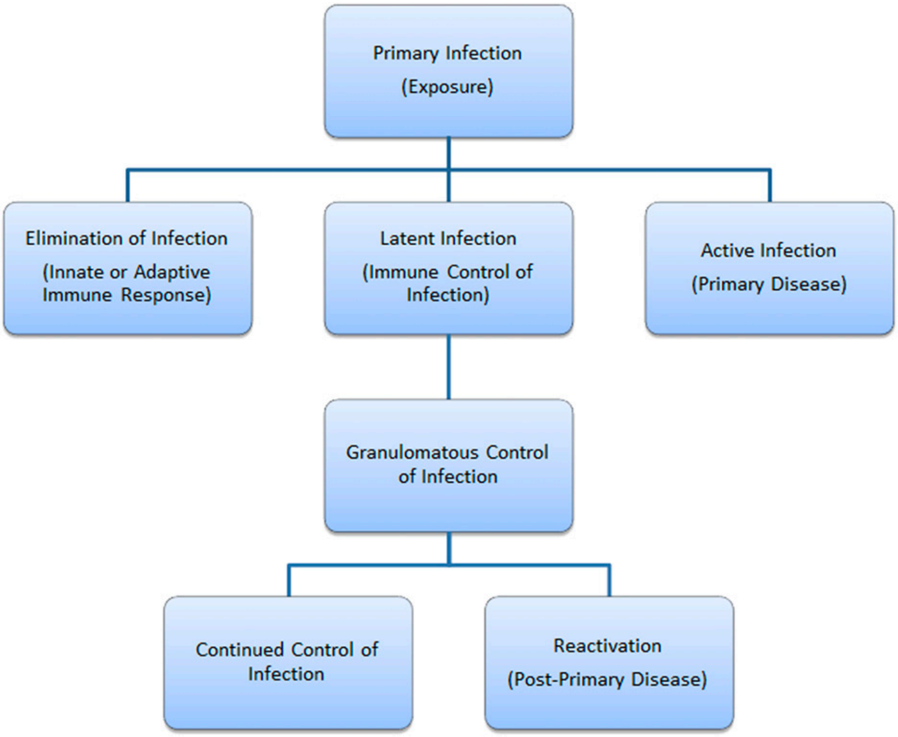

Figure. Outcomes of tuberculosis exposure.

throughout the world. (4) Newly diagnosed TB infection in a child is considered a sentinel event that indicates recent transmission of Mtb and should prompt investigation for the source TB case.

As the number of TB cases has declined in the United States, TB control efforts have shifted from identification and treatment of individuals with TB disease to identification and treatment of individuals with LTBI because latent organisms can reactivate and cause TB disease later in life. The US Centers for Disease Control and Prevention (CDC) approach for elimination of TB emphasizes the need to assess patients for risk of TB infection, test them appropriately, and treat those with LTBI to prevent the development of disease. (23)

The CDC currently recommends screening for TB infection only in children with risk factors for TB, including birth, travel, or previous residence outside of the United States, and close contact with an individual with infectious TB. (23) The American Academy of Pediatrics recommends assessing a child for TB risk factors at the first health-care visit, every 6 months during the first year, and then annually thereafter by asking questions about location of birth, travel history, and exposure to individuals with a history of TB disease, incarceration, homelessness, and foreign travel. (24) A tool has been developed by the Pediatric Tuberculosis Collaborative Group to aid TB risk assessment. (25) Foreign-born children who should be screened for TB include international adoptees, refugees, and immigrants. Screening requirements for immigrants before arrival in the United States vary by age. Immigrant children 2 to 14 years of age from countries with high TB prevalence should have a tuberculin skin test (TST) or interferon-γ release assay (IGRA), and any child with a positive TST or IGRA result should have a CXR obtained before arrival in the United States. Children younger than 2 years are not routinely tested for TB before immigration. Children aged 15 years and older generally have a CXR, and if the findings are abnormal they should have sputum smears and cultures obtained, all before immigration. (24) (26)

DIAGNOSTIC TESTS FOR TB INFECTION IN CHILDREN

There are 2 kinds of tests to diagnose TB infection, both based on host response and not on detection of the organism. Neither test can distinguish between LTBI and active TB disease. The oldest and most commonly used test is the TST, in which a purified protein derivative is injected intradermally. Induration at the injection site within 48 to 72 hours indicates a delayed-type hypersensitivity reaction and infection with Mtb. The size of induration combined with risk factors for TB is used to determine positive or negative TST test results (Table 2). Receipt of the Bacille Calmette-Guérin (BCG) vaccine should not affect what size TST induration is considered positive. Although the TST has many advantages, including vast clinical experience, provider familiarity with the test, and low cost, it has technical and logistical disadvantages. False-positive TSTs can occur due to infection with nontuberculous mycobacteria (NTM) or previous BCG vaccination. There is significant interobserver variation in TST result interpretation and TST placement, and TST assessment review requires 2 health-care visits. Many children do not return for the second visit to have the TST read. False-negative TST results can also occur in patients with recent infection before a robust immune response has developed, in very young children, in those who are malnourished or immunosuppressed, and in children with recent measles infection or vaccination.

Since 2005, IGRAs have been Food and Drug Administration (FDA) approved to diagnose LTBI in the United States. IGRAs are based on measurement of IFN-γ production in response to in vitro T-cell stimulation after exposure to Mtb antigens. Because IGRAs do not involve antigens from *M bovis* or common NTM species, false-positive IGRAs are less likely to occur from previous BCG vaccination or NTM infection. IGRAs also have operational advantages, including requiring a single health-care visit, a faster turnaround time than a TST, and standardized cutoff values that eliminate interobserver variation in test interpretation. IGRAs are also run with positive and negative controls to confirm adequate immunologic function. However, IGRAs are more expensive than the TST and require venipuncture. Two commercially available IGRAs exist: QuantiFERON-TB gold in-tube (Qiagen, Germantown, MD) and the T-SPOT.*TB* (Oxford Immunotec USA Inc, Marlborough, MA). Characteristics and test performance of the TST and IGRAs are compared in Table 3. Overall, IGRAs are at least as sensitive as, and more specific for, Mtb infection than the TST. (29)(30)(31)(32) Despite the advantages of IGRAs over the TST, the uptake of IGRAs by pediatric providers has been variable, likely because of lack of familiarity with the test. (33)

A recent joint guideline from the American Thoracic Society, the Infectious Diseases Society of America, and the CDC recommends use of an IGRA rather than a TST in children 5 years and older who require testing for TB. In children younger than 5 years, these guidelines recommend use of a TST. (23) However, based on more recent data, the American Academy of Pediatrics has expanded use of IGRAs to children as young as 2 years, (28) particularly in those who are BCG-vaccinated or unlikely to return for a TST reading visit. There are few data on IGRA performance in infants and very young children, so TST remains the preferred strategy to evaluate children younger than 2 years. Some experts prefer using IGRAs in BCG-vaccinated older children to eliminate the chance of false-positive TST results from vaccination. Some also suggest using both TST and IGRAs in situations where maximal sensitivity is needed and then

TABLE 2. **Definition of Positive Tuberculin Skin Test Results in Children (24)(27)**

INDURATION ≥5 MM	INDURATION ≥10 MM	INDURATION ≥15 MM
Clinical evidence of TB disease	Recent immigration from a high-prevalence[a] country	Age ≥4 y without any risk factors
Close contact with a person with known or suspected TB disease	Children exposed to individuals who are infected with HIV, injectable drug users, incarcerated individuals, or residents of nursing homes	
Radiographic changes consistent with active or previous TB	Medical conditions such as lymphoma, diabetes, renal failure, and malnutrition	
Immunosuppression due to medications, immunosuppressive conditions, or HIV infection	Age <4 y	

HIV=human immunodeficiency virus, TB=tuberculosis.

[a] Countries with a high absolute burden of incident TB cases according to the World Health Organization.

TABLE 3. **Comparison of the TST and IGRAs**

CHARACTERISTIC	TST	IGRAS
Recommended age, y	All	>2 (28); >5 (23)
Cross-reactivity with BCG	Yes	No
Cross-reactivity with NTM species (23)	Yes	Little[a]
Sensitivity, % (29)(30)	67–81	57–76
Specificity, % (29)(30)	79–92	85–98
Testing variability	Yes, interobserver variation	No, fixed cutoff value
Distinguish LTBI versus disease	No	No
Health-care encounters, No.	2	1
Venipuncture	No	Yes
Cost	Low	Higher
Laboratory capacity	No	Yes
Turnaround time, h	48–72	24
Can be falsely negative in immunosuppressed patients	Yes	Yes

BCG=Bacille Calmette-Guérin, IGRA=interferon-γ release assay, LBTI=latent tuberculosis infection, NTM=nontuberculous mycobacteria, TST=tuberculin skin test.

[a] *IGRAs can be positive after exposure to* Mycobacterium flavescens, Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium szulgai, *and other species in the* Mycobacterium tuberculosis *complex (*Mycobacterium africanum, Mycobacterium bovis, Mycobacterium canetti, *and* Mycobacterium microti).

treating for LTBI if either test is positive. Examples of this are an immunocompromised child who is at high risk for LTBI reactivation, or a child in close contact with a contagious TB case. In children at low risk for LTBI, use of both TST and IGRA is generally not indicated and may lead to discordant test results that need to be interpreted on a case-by-case basis, focusing on epidemiologic risk factors and clinical context, often with the assistance of providers experienced in treating people infected with TB.

EVALUATION OF A CHILD FOR TB INFECTION OR DISEASE

All children being evaluated for TB infection or disease should have a careful history obtained to assess for epidemiologic risk factors for TB exposure along with a thorough physical examination. Children with pulmonary TB can have diverse clinical manifestations that vary by age. School-aged children may be relatively asymptomatic; infants may demonstrate failure to thrive, respiratory distress, organomegaly, or skin lesions; and older children may have respiratory symptoms similar to those seen in adults, including cough, dyspnea, hemoptysis, crackles (rales), wheeze, and fever. Generally, more symptoms are present in very young infants and adolescents compared with school-aged children. Extrapulmonary manifestations of TB vary by the site of disease. TB lymphadenitis may present as painless, nontender lymph node swelling without fever or other systemic symptoms. TB osteomyelitis may present as localized pain, fever, and refusal to ambulate or bear full weight on the affected extremity.

All children with suspicion of TB infection or disease should undergo a TST or an IGRA, depending on the child's age. Children who are symptomatic or at high risk for TB disease (eg, close contact with an individual with infectious TB) should have CXR performed, regardless of the TST or IGRA result. Asymptomatic children who do not have risk factors for TB acquisition should have a CXR performed only if the TST or IGRA result is positive. Generally, asymptomatic children with positive TST and IGRA results and normal CXRs are considered to have LTBI and are treated accordingly. Children with symptoms or abnormal CXR findings consistent with TB should have gastric aspirate or sputum samples sent for acid-fast bacillus (AFB) staining of smear and culture and in high-risk situations should be started on empirical multidrug TB treatment while awaiting culture results.

Evaluation and management of children with positive TST or IGRA results should be performed in conjunction with state or local public health departments.

TREATMENT OF TB EXPOSURE IN YOUNG OR IMMUNOCOMPROMISED CHILDREN

Children younger than 4 years and those who are immunocompromised are at high risk for progression from TB infection to TB disease. If such children are exposed to an individual with infectious TB they should receive "window prophylaxis" or anti-TB therapy, usually with isoniazid (INH), even if initial TST or IGRA results are negative because delayed-type hypersensitivity reactions may not be detectable until several weeks to months after TB exposure. As part of routine contact investigation, repeated TST or IGRA is performed 8 to 10 weeks after contact with the source case ends. If repeated test results are negative, window prophylaxis can be discontinued. If repeated TST or IGRA results are positive, the child will need a thorough medical evaluation and CXR to assess for TB infection or disease.

TREATMENT OF LTBI IN CHILDREN

A variety of drugs and regimens are available for the treatment of LTBI in children. (34)(35) (Table 4) A single daily dose of INH for 9 months is the preferred regimen for treatment of LTBI in children known to or deemed to have INH-susceptible infection. (34)(36) Alternative regimens include 4 months of daily rifampin (RIF), 3 months of daily INH and RIF, and a 3-month, once-weekly dose of INH and rifapentine. (34)(35)(37) These shorter regimens have been shown to be as effective and as well tolerated as 9 months of INH therapy, with significantly higher completion rates. (38)(39)(40)(41)(42) However, the once-weekly INH and rifapentine regimen should not be used in children younger than 2 years because the safety and pharmacokinetics of this regimen have not been established for this age group. Furthermore, because the once-weekly INH and rifapentine regimen is administered intermittently at weekly intervals, and because missed doses could jeopardize efficacy or safety, directly administered therapy (DOT) is recommended.

The optimal treatment for LTBI in children exposed to drug-resistant, particularly multidrug-resistant, TB is unknown. (43)(44)(45)(46) When monoresistance to INH or RIF is likely, INH or RIF, whichever drug is effective, can be used, similar to what was detailed previously herein. In patients with exposure to multidrug-resistant TB, options include close observation without therapy using a fluoroquinolone if presumed fluoroquinolone susceptible, or combination drug regimens such as pyrazinamide (PZA) and ethambutol (EMB). (47)(48)(49)(50) The optimal duration for any of these regimens is undefined. Infants who are exclusively breastfeeding and receiving INH, or whose mother is receiving INH, should receive a multivitamin to minimize the risk of neurologic toxicity associated with INH.

TREATMENT OF ACTIVE TB IN CHILDREN

In general, the principles of treatment and the drugs used for the treatment of TB in children are the same as in adults. (51)(52) Treatment of extrapulmonary TB, except for TB meningitis, in children is generally similar to the treatment of pulmonary disease. Drugs for the treatment of TB in children are shown in Table 5.

Laboratory confirmation of TB in children (in particular, children <5 years of age) is challenging because of the paucibacillary nature of their disease and because of the

TABLE 4. **Treatment Regimens for Latent Tuberculosis Infection in Children**

DRUG	DOSE	DURATION, MO	INTERVAL
Isoniazid	10–15 mg/kg 20–30 mg/kg	9	Daily Twice weekly
Isoniazid and rifapentine	Isoniazid: 10–15 mg/kg Rifapentine: 10–14 kg: 300 mg >14–25 kg: 450 mg >25–32 kg: 600 mg >32–49 kg: 750 mg >50 kg: 900 mg	3	Once weekly
Rifampin	10–20 mg/kg	4	Daily

TABLE 5. **Antituberculous Drugs**

GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
Isoniazid	Amikacin	Levofloxacin	Ethionamide	Linezolid
Rifampin	Capreomycin	Moxifloxacin	Cycloserine	Clofazimine
Pyrazinamide	Kanamycin		Para-aminosalicylic acid	High-dose isoniazid
Ethambutol	Streptomycin			Amoxicillin/clavulanate
				Imipenem
				Clarithromycin
				Thiacetazone
				Bedaquiline
				Delamanid
First line	Second line	Second line	Second line	Third line

difficulties in obtaining specimens for culture. In addition, TB can rapidly advance and pose serious risk to life in young children. For these reasons, a presumptive diagnosis should be made on epidemiologic, clinical, and radiographic grounds, and empirical treatment should be promptly initiated. A 4-drug combination of INH, RIF, PZA, and EMB is the recommended first-line regimen. The duration of such treatment that has been empirically initiated depends on the clinical course, radiographic changes, and identification of alternative diagnoses.

For drug-susceptible TB, a 4-drug regimen of INH, RIF, PZA, and EMB for 2 months followed by a 2-drug regimen of INH and RIF for an additional 4 months is recommended. Programmatically, treatment should be administered under the DOT approach; parents should not supervise DOT for their children. Contrary to the practice in the treatment of TB in adults, where pyridoxine supplementation is recommended during INH therapy to prevent the development of peripheral neuropathy, this is necessary only in children with nutritional deficiencies, with symptomatic HIV infection, or who are breastfeeding.

DRUG-RESISTANT TB

Drug-resistant TB defines infection caused by strains of Mtb resistant to at least 1 of the first-line anti-TB drugs: INH, RIF, PZA, or EMB. Multidrug-resistant TB denotes Mtb that is resistant to at least INH and RIF. Extensively drug-resistant TB refers to Mtb resistant to at least INH and RIF plus any resistance to the fluoroquinolones or injectable anti-TB agents.

In young children, drug-resistant TB is primarily a consequence of transmission of drug-resistant TB to the child rather than a reflection of previous exposure to TB treatment. Drug-resistant TB is essentially a microbiological diagnosis; there are no clinical or radiologic clues to distinguish it from drug-susceptible TB. Therefore, when drug-resistant TB is suspected, every effort should be made to obtain specimens for culture and drug susceptibility testing. In situations in which microbiologic confirmation of resistant TB is lacking, resistance can be inferred from the drug susceptibility profile of a known adult contact, if available. If no drug susceptibility is available for the child or an adult contact, drug resistance may be inferred if the child is failing therapy (clinical or radiographic worsening). In such cases, treatment decisions may have to be based on the prevailing regional resistance pattern in Mtb isolates.

In general, the principles of the treatment of drug-resistant TB in children are similar to those of adults. (53)(54)(55) When possible, drug susceptibility test results should drive the regimen selection. A single drug should never be added to a failing regimen. Depending on the degree of resistance, the regimen used should consist of at least 4 drugs to which the child or the adult contact is naive or their isolates are susceptible. All treatment should be given daily through DOT, ideally with the oversight of the local public health department. Management includes monthly monitoring for adherence, response to treatment, and adverse events. Direct evidence informing optimal duration of treatment for drug-resistant TB in children is lacking. Therefore, treatment duration is adopted from guidelines for the treatment of TB in adults. Often, second- and third-line TB medications have more adverse effects than first-line medications.

Summary

- Based on research evidence and consensus, newly diagnosed tuberculosis (TB) infections in children are sentinel events that indicate recent transmission of *Mycobacterium tuberculosis* (Mtb) and require prompt investigation for the source TB case. (24)
- Based on research evidence and consensus, screening for TB infection should be performed only in children with risk factors for TB (including birth, travel, or previous residence outside of the United States, and close contact with an individual with infectious TB) using a questionnaire. (24)
- Based on strong research evidence, interferon-γ release assays (IGRAs) have several advantages over the tuberculin skin test (TST), including higher specificity and lower likelihood of false-positive results due to previous Bacille Calmette-Guérin vaccination or nontuberculous mycobacteria infection. (23)
- Due to insufficient evidence, the youngest age at which IGRAs are reliable is not clear. The American Thoracic Society/Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America consensus guidelines favor use of the TST rather than IGRAs in children younger than 5 years. (23) However, the American Academy of Pediatrics recommends the use of IGRAs in children as young as 2 years old in some circumstances. (28) The TST remains the preferred strategy to evaluate children younger than 2 years for TB infection due to limited data regarding the use of IGRAs in this age group.
- Based on research evidence and consensus, children younger than 4 years and those who are immunocompromised are at high risk for progression from TB infection to TB disease, and if exposed to an individual with infectious TB require "window prophylaxis," usually with isoniazid (INH), even if initial TST or IGRA test results are negative.
- Based on strong research evidence, a shorter (3-month) treatment regimen for latent TB infection in children older than 2 years and using once weekly INH and rifapentine administered via directly observed therapy has high rates of efficacy and adherence. (56)
- Based on research evidence and consensus, treatment of TB disease in children requires multidrug therapy for a minimum of 6 months, depending on the site of infection and drug susceptibility of the Mtb isolate. Treatment for TB should be provided via directly observed therapy through local or state public health departments. (52)

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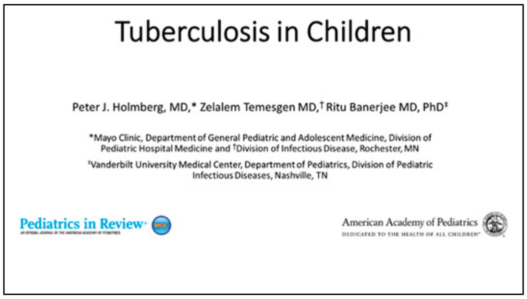

Tuberculosis in Children

Peter J. Holmberg, MD,* Zelalem Temesgen MD,† Ritu Banerjee MD, PhD‡

*Mayo Clinic, Department of General Pediatric and Adolescent Medicine, Division of Pediatric Hospital Medicine and †Division of Infectious Disease, Rochester, MN

‡Vanderbilt University Medical Center, Department of Pediatrics, Division of Pediatric Infectious Diseases, Nashville, TN

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1. An 8-year-old girl with Crohn disease has a positive interferon-γ release assay (IGRA) result before being started on a tumor necrosis factor antagonist. She has been afebrile and is not coughing. Her chest radiograph is normal, and she is diagnosed as having latent tuberculosis infection (LTBI). Exposure to which of the following contacts is the most likely source from which she acquired *Mycobacterium tuberculosis* (Mtb)?
   A. An 8-year-old classmate with cough and congestion who immigrated to the United States from South Korea 9 months earlier.
   B. An 8-year-old classmate who was born in Romania and was treated for LTBI at 3 years of age.
   C. Her 42-year old uncle who was recently diagnosed as having active TB.
   D. Her 7-year-old cousin who traveled to Mexico 2 years ago.
   E. Her 2-year-old brother who has had intermittent cough and wheezing.
2. A 16-year-old boy is applying to be a hospital volunteer and the hospital requires a TB screening test. He is well and immigrated to the United States from India when he was 3 years old. He received Bacille Calmette-Guérin vaccine as an infant. He returned to India 3 years ago to visit family. Which of the following is the most appropriate next step in management?
   A. Chest radiography.
   B. Gastric aspirate for Mtb polymerase chain reaction.
   C. IGRA.
   D. Induced sputum for acid-fast bacillus (AFB) smear and culture.
   E. Tuberculin skin test (TST).
3. A healthy 15-month-old girl is brought to the office by her mother who states that the girl's paternal grandmother was diagnosed as having active TB the past week and has been started on multidrug treatment. The paternal grandmother has had close contact with the girl during the past 2 months when she moved close to the family. The paternal grandmother has no history of being treated for TB. A TST is placed on the girl. Which of the following is the most appropriate next step in management?
   A. Begin isoniazid therapy.
   B. Begin isoniazid therapy if her TST shows at least a 15-mm induration.
   C. Begin isoniazid, rifampin, and ethambutol therapy.
   D. Obtain gastric aspirate the next 3 mornings for AFB smear and culture.
   E. Obtain gastric aspirate the next 3 mornings for AFB smear and culture and begin isoniazid, rifampin, pyrazinamide, and ethambutol therapy.
4. A healthy 14-year-old boy is brought to the office due to concern for TB exposure. His aunt who lives in Bangladesh visited the family 2 months ago for a week and had a cough at that time. When she returned to Bangladesh she was diagnosed as having active TB that was isoniazid-resistant but susceptible to rifampin, ethambutol, pyrazinamide, linezolid, and amikacin. The boy feels well and has not had fever or cough. The IGRA results are positive. Findings on a chest radiograph are normal. Which of the following is the most appropriate next step in management?
   A. Daily ethambutol therapy for 9 months.
   B. Daily isoniazid therapy for 9 months.
   C. Daily rifampin therapy for 4 months.
   D. Weekly ethambutol and linezolid therapy for 6 months.
   E. Weekly isoniazid and pyrazinamide therapy for 6 months.

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5. A 2-year-old boy is admitted to the hospital with a 1-day history of left-sided hemiparesis and a 2-week history of fever and intermittent cough. He attends child care and his child care provider has had a persistent cough. A chest radiograph shows a right lower lobe infiltrate and hilar adenopathy. IGRA results are positive. Cerebrospinal fluid Mtb polymerase chain reaction is positive, and AFB culture is pending. Gastric aspirate AFB cultures are also pending. Which of the following is the most appropriate initial treatment?

   A. Amikacin, pyrazinamide, and ethambutol.
   B. Amikacin, pyrazinamide, ethambutol, rifapentine, and rifampin.
   C. Ethambutol and linezolid.
   D. Isoniazid, rifampin, pyrazinamide, and ethambutol.
   E. Rifampin and isoniazid.

Tuberculosis in Children

Peter J. Holmberg, Zelalem Temesgen and Ritu Banerjee

Pediatrics in Review 2019;40;168

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Nontuberculous Mycobacterial Infections in Children

Jyotsna Bhattacharya, MD,* Sindhu Mohandas, MBBS,* David L. Goldman, MD†

*Department of Pediatric Infectious Diseases and †Department of Pediatrics and Microbiology and Immunology, Children's Hospital at Montefiore/Albert Einstein College of Medicine, Bronx, NY

Education Gaps

1. Outbreaks of nontuberculous mycobacterial infections have been increasingly reported following cosmetic procedures performed abroad. Failure to recognize this association can lead to inappropriate or delayed therapy. (1)
2. The emergence of drug resistance in specific species of nontuberculous mycobacteria infections (especially *Mycobacterium abscessus*) complicates medical therapy. Appropriate treatment of these infections involves the identification of a specific species and drug resistance testing. (2)

Objectives

After completing this article, readers should be able to:

1. Recognize the major clinical features associated with nontuberculous mycobacteria (NTM) infections in children.
2. Recognize that NTM infections are a potential risk related to medical tourism for cosmetic surgery.
3. Understand the strengths and weaknesses of currently available diagnostic methods.
4. Plan the appropriate management of NTM infections based on the specific clinical presentation and mycobacterial species.

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ABBREVIATIONS

AFB	acid-fast bacillus
CF	cystic fibrosis
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
IFN-γ	interferon-γ
IGRA	interferon-γ release assay
IRIS	immune reconstitution inflammatory syndrome
MAC	*Mycobacterium avium* complex
MALDI-TOF	matrix-assisted laser desorption/ionization–time of flight
NTM	nontuberculous mycobacteria
RGM	rapidly growing mycobacteria
SGM	slowly growing mycobacteria
SSTI	skin and soft tissue infection

INTRODUCTION

Nontuberculous mycobacteria (NTM) include all mycobacteria other than *Mycobacterium tuberculosis, Mycobacterium bovis,* and *Mycobacterium leprae*. Children are constantly exposed to NTM, yet clinical signs of infection are unusual. NTM exist primarily in the environment, causing human disease as opportunistic pathogens in the appropriate clinical context. Lymphadenitis is far and away the most common manifestation of NTM disease in children. Other, less common, manifestations include skin and soft tissue infections (SSTIs), lung infections, and disseminated disease. Since the last review of NTM disease in *Pediatrics in Review,* (3) several important developments have occurred, including changes in the epidemiology and treatment, which are reviewed herein.

MICROBIOLOGY AND CLASSIFICATION

Currently there are more than 170 recognized NTM species, although a limited number of species cause human disease. It survives inside amoeba, and the traits that promote this process may also allow for successful macrophage infection. (4) Several characteristics promote both persistence in the environment and human disease. The lipid mycolic acid outer membrane is responsible for the acid-fast bacillus (AFB) staining feature of NTM (Fig 1). It confers a hydrophobic nature to the organism, which has been linked to changes in organism aggregation and enhanced aerosolization. (5) The hydrophobic NTM membrane also promotes surface adherence and helps restrict entry of antibiotics and disinfectants into the cell. NTM form biofilms that promote surface attachment and persistence of the organism in water systems (ie, pipes, showerheads) and catheters. (6) Other traits that have been linked with the NTM persistence in the environment include the ability to grow in a variety of hostile conditions, such as low oxygen concentrations, low organic matter concentrations, high temperatures, and low pH. (7)(8)(9)

Typically, NTM are categorized by their growth characteristics into 2 categories: slowly growing (SGM) and rapidly growing (RGM) mycobacteria species. RGM demonstrate visible growth in culture media within 7 days, whereas SGM take weeks to exhibit growth. Certain species are particularly slow growers (eg, *Mycobacterium ulcerans* and *Mycobacterium genavense*) and may take 8 to 12 weeks to grow. (10) The NTM species commonly implicated in human disease are listed in Tables 1 and 2. Growth characteristics along with colony pigmentation are used to sort NTM into groups using the Runyon classification system. Definitive speciation of NTM isolates using standard microbiological techniques is often not possible. As a result, species with similar phenotypic characteristics have historically been grouped into complexes (ie, *Mycobacterium avium* and *Mycobacterium abscessus* complex). Newer molecular assays (see later herein) have led to improved discrimination of NTM at the species and subspecies levels.

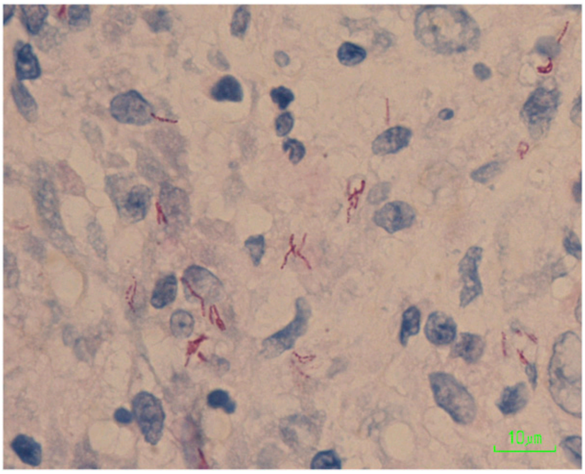

Figure 1. Acid-fast bacillus stain of tissue from a patient that subsequently grew *Mycobacterium chelonae*. (Image provided by Dr Michael Levi [Montefiore Hospital, Bronx, NY]).

EPIDEMIOLOGY

NTM are found in a wide range of environmental sites, and disease is acquired primarily through exposure to these sites, including soil and water (ie, drinking water, household plumbing, drainage waters, and natural waters). (6)(11) These organisms are easily aerosolized in droplets and also survive in dust particles, both of which serve as a source for pulmonary infection. Aerosols containing high densities of NTM are found around areas with splashing water, including sinks and showers. Human-to-human and animal-to-human transmissions are thought not to occur or to occur rarely. A recent whole genome sequencing study of respiratory NTM isolates indicates the possibility of human-to-human transmission, although more study is needed in this area. (12) Health-care–associated transmission can also occur after dental, surgical, and cosmetic procedures. (13)(14)

Pediatric studies during the past decade show NTM disease incidence rates ranging from 0.84 per 100,000 in Australia to 3.1 per 100,000 in Germany. (15)(16) Many but not all studies report an increasing incidence of NTM disease, although it is unclear whether this reflects a true increase in disease or a result of improved diagnostics. (17)(18)(19) An increase in the number of susceptible children due to new immunomodulatory therapies may have also contributed to this increased incidence. Seasonal variation in the incidence of NTM lymphadenitis and SSTIs with a higher incidence in the late winter and early spring has been reported. (20) Outbreaks of NTM disease can occur in both cystic fibrosis (CF) centers and in the context of contaminated medical equipment. (14)(21)

Severe NTM disease occurs with immunodeficiency and chronic lung disease. In immunocompromised children, NTM infections may present in both localized and nonlocalized forms. Effective immunity against

TABLE 1. **Slowly Growing Mycobacteria**

SPECIES	PULMONARY DISEASE	SSTI	PHYSICAL EXAMINATION
Mycobacterium avium complex	• Frequently isolated in patients with cystic fibrosis	• Most common cause of cervical adenitis	• Nodules, pustules, or plaques • Sinus tract and abscess formation
Mycobacterium kansasii	• More frequent in patients with HIV and older individuals with COPD • Similar to *Mycobacterium tuberculosis* disease • In the United States, more frequent in the South and Midwest	• Infrequent	• Nodules, pustules, ulcers, and abscesses • May resemble sporotrichosis
Mycobacterium marinum		• Exposure to fresh or salt water and marine animals • Swimming pool granuloma	• Solitary, red to violaceous papule or nodule that progresses to a shallow ulceration • Occasionally in a sporotrichotic distribution • Delay in diagnosis can lead to tenosynovitis, septic arthritis, and osteomyelitis
Mycobacterium ulcerans		• Buruli ulcer • Endemic in Africa, Southeast Asia, Australia, and South and Central America	• Chronic ulcerative skin disease

COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; SSTI=skin and soft tissue infection.

NTM involves a coordinated response among T cells, natural killer cells, and macrophages. Macrophage infection with NTM results in interleukin-12 production that stimulates interferon-γ (IFN-γ) by T cells and natural killer cells. In turn, IFN-γ activates macrophages to limit organism growth. Children with defects in T-cell immunity (ie, AIDS) or the interleukin-12/IFN-γ pathway are, therefore, at risk for severe disease. (22) An increased incidence of NTM infections has been observed in both hematopoietic stem cell and solid organ transplant recipients. Lung transplant recipients are disproportionately affected by NTM-associated pneumonia, presumably due to previous colonization of the donor lung and augmented immunosuppression. Similar to *M tuberculosis* infections, tumor necrosis factor–blocking agents seem to increase the risk of NTM infections, although additional studies are needed

TABLE 2. **Rapidly Growing Mycobacteria**

SPECIES	PULMONARY	SSTI	PHYSICAL EXAMINATION	OTHER
Mycobacterium abscessus complex	• Severe pneumonia in children with cystic fibrosis	• Commonly implicated • Medical tourism	• Multiple lesions that may be purple, persistent-drainage abscesses	• Three subspecies with different susceptibility patterns, especially to macrolides
Mycobacterium chelonae	• Colonization common • Disease rare	• Tattooing	• Multiple lesions	• Catheter-related infections
Mycobacterium fortuitum	• Colonization common • Less frequent cause of disease	• Surgical procedures • Puncture wounds • Footbaths • Pedicures	• More likely to present as a single lesion	• Catheter-related infections

SSTI=skin and soft tissue infection.

to better characterize this association. (10) In addition to immunodeficiency, children with chronic lung disease, especially those with cystic fibrosis (CF)– and non-CF–related bronchiectasis are at increased risk for NTM pulmonary disease. (23) The basis for this enhanced susceptibility is poorly understood but may be related to damage to the respiratory mucosa, which allows for increased adhesion by the organism and changes in the local microbiota. (24)(25) Because of the close association between NTM and non-CF bronchiectasis, some have hypothesized that NTM infection may actually cause bronchiectasis (reviewed in the article by Bonaiti et al [26]). Other forms of chronic respiratory disease that have been associated with NTM infection include conditions that are more common in adults, such as α_1-antitrypsin deficiency chronic obstructive pulmonary disease, α_1-antitrypsin anomalies, Lady Windermere syndrome, and pneumoconiosis (reviewed in the article by Chan and Iseman [27]). Risk factors for NTM disease are shown in Table 3.

NTM INFECTIONS

Lymphadenitis

Chronic cervicofacial adenitis (affecting the superior anterior cervical or submandibular nodes) is the most common manifestation of NTM adenitis. Less commonly, posterior cervical nodes may also be involved. (28) NTM adenitis outside the cervicofacial region (ie, axillary and inguinal nodes) is described but is relatively uncommon (1.6% of all cases in 1 study). (29) The precise mechanism by which the organism is acquired from the environment and comes to infect the lymph node is poorly understood. Infection typically occurs in children aged 1 to 5 years and progresses over weeks to months in a subacute manner. NTM adenitis is generally unilateral and not associated with fever or systemic symptoms. (20)(30) This contrasts with *M tuberculosis* adenitis, which tends to occur in older children and adolescents and is often associated with systemic symptoms. Local signs and symptoms of NTM adenitis include firmness, erythema, fluctuance with a violaceous skin discoloration, and even fistula formation. Typically, NTM adenitis is less painful than bacterial adenitis. Suppuration with the development of chronic sinus tracts may complicate NTM adenitis and also cause damage to the facial nerve, especially with preauricular disease. (28) The diagnosis (see later herein) is usually made in the context of children who are initially treated with antistaphylococcal antibiotics but who do not respond appropriately. The most common species of NTM causing adenitis in the United States belong to the MAC group, which includes *M avium* and *Mycobacterium intracellulare*. A variety of other species have been reported to cause adenitis, including but not limited to *Mycobacterium scrofulaceum*, *Mycobacterium haemophilum*, *Mycobacterium malmoense*, and *Mycobacterium kansasii*. (20)

NTM Skin and Soft Tissue Infections

The next most common form of pediatric NTM disease, SSTIs, occur in both healthy and immunocompromised children. SSTIs secondary to NTM typically exhibit less erythema and tenderness compared with pyogenic infections. Both RGM and SGM cause skin and subcutaneous tissue infections (Fig 2). NTM SSTIs usually result from direct inoculation of the organism into soft tissue. The most common portals of entry are skin abrasions, open injuries, fractures, surgical or injection sites, puncture wounds (stepping on a nail), and even combat-related injuries (ie, high-impact blast) with environmental wound contamination. (31) Abscess formation, which may be painful, and drainage can occur at the affected site, especially with infections due to RGM species. Importantly, skin involvement may be a

TABLE 3. **Risk Factors for NTM Disease**

LUNG CONDITION	IMMUNOLOGIC DEFECTS	EXPOSURE TO HIGH NTM CONCENTRATIONS
Cystic fibrosis	HIV/AIDS	Nosocomial exposures (medical equipment)
Non–cystic fibrosis bronchiectasis	Common variable immunoglobulin deficiency syndrome	Showerheads, indoor hot tubs, water heater temperatures ≤122°F (≤50°C)
α_1-antitrypsin deficiency	Genetic defects in interferon-γ receptors or interleukin-12	Potting soils, particularly those enriched with peat
Pulmonary alveolar proteinosis	Biological anti-inflammatory agents	Livestock, seawater

HIV=human immunodeficiency virus; NTM=nontuberculous mycobacteria.

representation of disseminated disease in immunocompromised hosts.

Direct inoculation may result in localized infections at other sites, including tendon sheaths, bursae, joints, and bones. *Mycobacterium marinum* is the most common NTM that causes tenosynovitis, with infection usually involving the hands and wrists. (32) Other NTM that cause tenosynovitis include *Mycobacterium fortuitum*, *M abscessus*, *Mycobacterium chelonae*, and *M kansasii*. Deep tissue infections have been reported after cardiac surgery, including osteomyelitis of the sternum. (33)

Cosmetic Procedures. Recently, RGM infections have increasingly been reported after cosmetic procedures performed abroad in developing countries. (34)(35)(36) In these instances, infection is likely acquired as a result of a breeched sterile procedure and exposure to nonsterile water. A multistate US outbreak was reported in 2013 with 21 cases of NTM infections after cosmetic procedures performed in the Dominican Republic. The procedures included liposuction, breast surgery, buttock augmentation, and abdominoplasty. Thirteen of the 21 patients had the procedures performed at the same clinic. The most common cause of the infection was *M abscessus,* followed by *M fortuitum.* (34) Patients with these types of infection can present with deep-seated or superficial wound infections with tender erythematous nodules, pustules, and abscesses. Systemic signs and symptoms are usually less prominent. The wounds usually involve the incision sites with raised granulomatous tissue. Erythema, wound dehiscence, and purulence may be present (Fig 3).

Affected patients are often unsuccessfully treated for other bacterial disease before a diagnosis of RGM SSTI is considered. These infections have nonspecific clinical features, and a high index of suspicion is necessary to correctly diagnose, treat, and limit the spread of disease. When clinicians suspect RGM infection in medical tourists, adequate specimens should be collected in addition to notifying the laboratory so that special techniques can be used for optimal recovery of these organisms: *M chelonae, M fortuitum*, and *M abscessus*. Also, SSTIs have been reported in association with nonsurgical cosmetic procedures. *M chelonae* and *M abscessus* infections have been described with tattooing. *M haemophilum* infection has been described with permanent eyebrow makeup. (37)(38)

Buruli Ulcer. *M ulcerans* is an extremely common mycobacterial disease worldwide and is the cause of Buruli ulcer. This diagnosis should be considered in travelers, especially to tropical regions. Most cases are reported from West and Central Africa and Australia. (39) *M ulcerans* infection usually begins as a painless nodule or papule on an

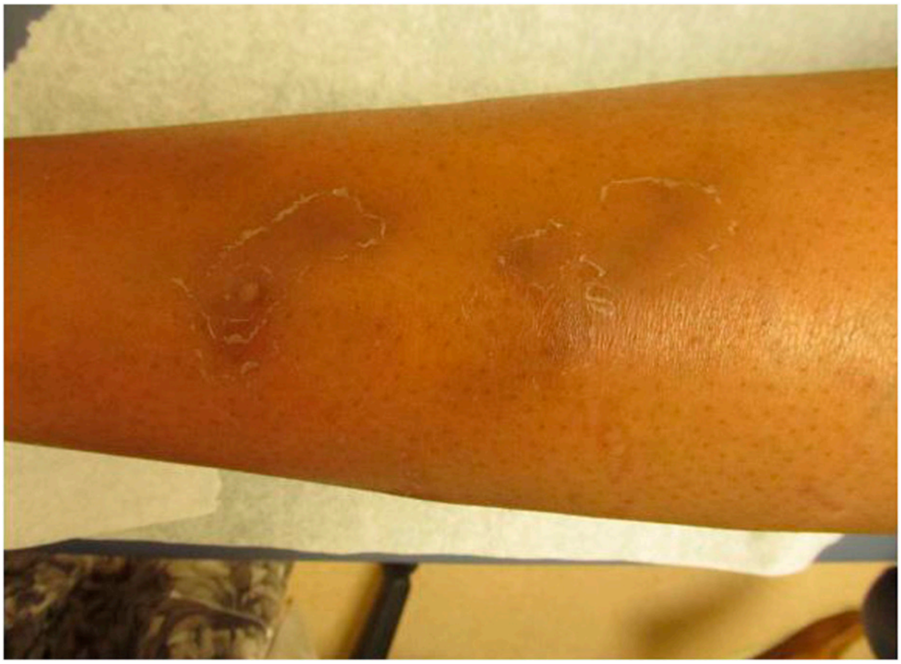

Figure 2. A 17-year-old girl with systemic lupus erythematosus receiving immunosuppressive therapy presented with erythematous palpable nodules of the lower extremity. Pathology was significant for necrotizing granuloma. A tissue block was sent to the Centers for Disease Control and Prevention (CDC) and was confirmed by polymerase chain reaction and sequencing to be *Mycobacterium chelonae* infection. (Image provided by Dr Diana H. Lee [Children's Hospital at Montefiore, Bronx, NY]).

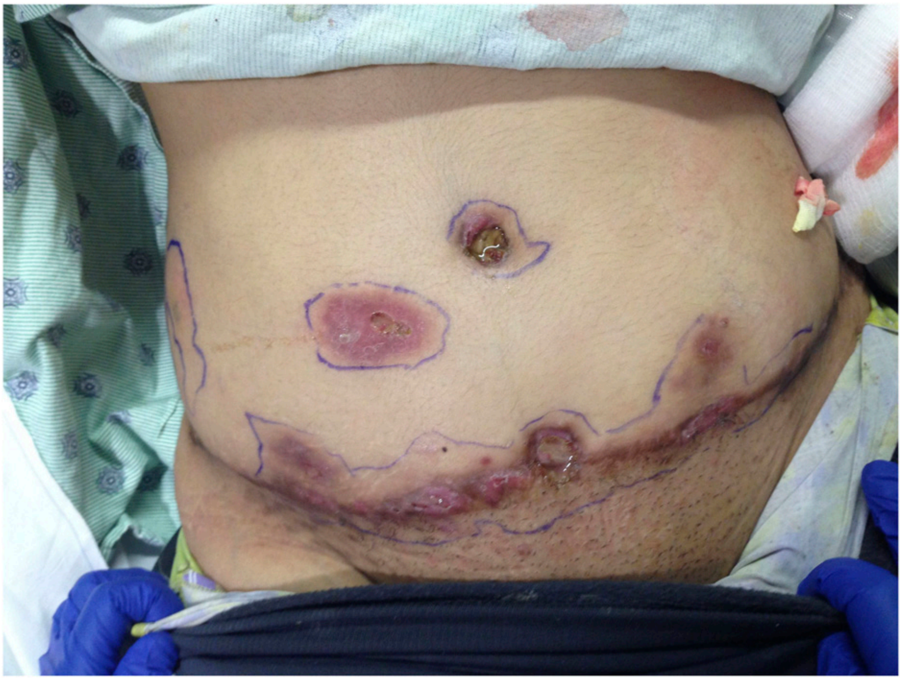

Figure 3. *Mycobacterium abscessus* infection in a 20-year-old woman after abdominoplasty performed in the Dominican Republic. Wound along the horizontal incision site is notable for induration and heaped up granulomatous tissue, with areas of erythema and wound dehiscence. Purulent drainage is seen around the reconstructed umbilicus. (Image provided by Sindhu Mohandas [Children's Hospital at Montefiore, Bronx, NY]).

extremity that goes on to ulcerate. Primary involvement of the head, neck, and genitals also occurs. The hallmark of this disease is extensive ulceration leading to scarring, limb contractures, and disfigurement. Antimicrobial drug treatment for *M ulcerans* infection may produce an initial clinical worsening before a positive response. (40)

Pulmonary Infections

CF- and Non-CF–Associated Bronchiectasis. NTM pulmonary disease most often occurs in children with preexisting lung disease, especially CF, and children with non-CF–related bronchiectasis or immunodeficiency. Infections in lung transplant recipients are also well described. (41) Pulmonary NTM infection is rare in otherwise healthy children. The potential for outbreaks of NTM pulmonary disease in CF centers has been highlighted in recent studies. (12)(42) Most children have fever, weight loss, and fatigue. In children with underlying lung disease, increasing cough, sputum production, waning exercise intolerance, and deterioration in pulmonary function may be indications of pulmonary NTM disease. (43)(44) The most frequently isolated NTM in patients with CF is MAC, followed by *M abscessus* complex, although the relative proportions of these isolates vary by geographic area. (43)(44) In general, *M abscessus* pulmonary infections tend to be more virulent than MAC infections and are more likely to be associated with invasive disease and deterioration of pulmonary function. A range of radiologic features has been reported in association with pulmonary NTM disease. In children with CF, small pulmonary nodules with bronchiectasis is the most common radiologic presentation. (45) A tree-and-bud pattern may also be present on computed tomographic scans, reflecting bronchiolar disease. Importantly, these features are not specific for NTM and can be seen with infections secondary to a variety of pathogens. Other radiologic presentations of NTM lung disease include fibrocavitary lesions (indistinguishable from *M tuberculosis* disease) and large nodules that can be confused with malignancy. (45)(46)

Hot Tub Lung. A hypersensitivity pneumonitis, also known as hot tub lung, occurs in immunocompetent adults and children after bathing in hot tubs, where NTM are well suited to grow. Aerosolization of NTM by water jets can result in high inocula exposures, and in some individuals, an overexuberant inflammatory response ensues. (47)(48) The radiologic appearance of hot tub lung is extensive ground glass opacification or consolidation along with centrilobular nodularity.

Disseminated Disease

Disseminated NTM infections typically occur in immunocompromised children, including those with a defect in cellular immunity and in the gamma interferon pathway. Other conditions associated with disseminated NTM infection include hematologic malignancy and the immunosuppression used for organ transplant recipients. During the AIDS epidemic, the incidence of disseminated disease dramatically increased in both children and adults. (49) However, with the introduction of highly active antiretroviral therapy (HAART), the incidence has greatly decreased.

The most common NTM associated with disseminated disease is MAC (>90%). (10)(50) In children with human immunodeficiency virus (HIV) infections, disseminated MAC occurs in the context of extremely depressed T-cell numbers. Disseminated disease may occur in the context of SSTIs and pulmonary infections, especially those secondary to NTM rapid growers. Skin lesions may be the earliest manifestation of disseminated disease in immunocompromised patients.

NTM-Associated Immune Reconstitution Inflammatory Syndrome. NTM-associated immune reconstitution inflammatory syndrome (IRIS) occurs in immunosuppressed individuals and results from an enhanced immune response (in the context of HAART or reduction of immunosuppression in organ transplant recipients) against residual NTM organisms or antigens. NTM-related IRIS should be considered in the first few weeks to months after starting antiretroviral therapy. (51) Affected individuals may or may not have a previous diagnosis of NTM infection. Common presentations include lymphadenitis (peripheral, intrathoracic, or intra-abdominal), fever, and night sweats. IRIS may also present as pulmonary infiltrates and hepatosplenomegaly. (52)

Catheter-Associated Infections. Biofilm formation along with environmental contamination and inadequate sterilization procedures promote catheter- and medical device–associated infections. A systematic breakdown in infection control procedures can lead to outbreaks of disease. (53)(54) This situation must be carefully distinguished from pseudo-outbreaks, in which laboratory contamination of specimens results in repeated positive cultures. (55) Catheter-associated bloodstream infections secondary to NTM occur in both immunocompetent and immunocompromised patients (especially those with hematologic malignancies). (56) These infections are often due to RGM (ie, *Mycobacterium mucogenicum, M fortuitum,* and *M abscessus*). (10)(57) Most patients are febrile but not necessarily neutropenic. (58) Catheter-associated infections may also result in peritonitis and exit site infections in children receiving peritoneal dialysis. (59)(60) In patients with ventriculoperitoneal shunts, meningitis can occur. (61) Recently, invasive NTM disease has been reported in association with the use of heater-cooler devices during cardiothoracic surgery. (62)

DIAGNOSIS

AFB (Ziehl-Neelsen or Kinyoun methods) and fluorochrome staining are used to detect mycobacterial organisms in tissue, with the latter technique being more sensitive. Tuberculin skin testing has been reported to have a wide range of sensitivity (30%–60%) in the diagnosis of NTM disease (reviewed in the study by Zimmermann et al [63]). This assay has limited utility in distinguishing between NTM and *M tuberculosis* infections. An interferon-γ release assay (IGRA) is more specific than tuberculin skin testing and is useful in differentiating tuberculous and NTM infections, especially in areas with a low prevalence of tuberculosis. (64)(65) For most NTM infections, including MAC, the results of the QuantiFERON test (Qiagen, Hilden, Germany) should be negative. However, false-positive results have been described for specific strains of NTM that express specific antigens with substantial homology to those expressed by *M tuberculosis.* (66)(67)(68) Furthermore, interpretation of both tuberculin skin testing and IGRA assays is not possible in the context of simultaneous infections with both pathogens, which occurs more frequently in areas of high tuberculosis prevalence. (66) For children younger than 5 years, who are most likely to have NTM lymphadenitis, there are limited data on the utility of IGRAs.

Specimens for NTM isolation are cultured using both solid and liquid media. For nonsterile specimens, decontamination should be performed to prevent bacterial or fungal overgrowth. Certain NTM species may be difficult to grow in the laboratory because they have specific nutritional requirements, requiring media supplementation. In addition, individual species may grow very slowly. Thus, the laboratory should be alerted when NTM disease is being considered. Strict adherence to laboratory protocols is necessary for processing culture specimens because laboratory contamination (especially with tap water) is a well-recognized cause of pseudo-outbreaks. (55)(69)

The gold standard for diagnosis is the isolation of the organism in culture, which also allows for drug susceptibility testing. However, a negative culture does not exclude disease (Table 4). Multiple molecular methods have been developed to detect NTM. Polymerase chain reaction probes that allow for detection of organisms in fixed and unfixed tissue specimens are commercially available for some species (eg, MAC, *M kansasii*, and

Mycobacterium gordonae), but not all. Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) has been studied for the diagnosis and differentiation of NTM species, although specific species and subspecies identification is limited. (70)(71) 16S rRNA gene sequencing is useful in these circumstances, but occasionally multigene (ie, *hsp65*, *rpoB*, and *secA*) or whole genome sequencing is needed for definitive identification of certain species and subspecies. (71)(72)(73) Species/subspecies identification can be critical in guiding initial treatment. For example, among *Mycobacterium abscessus* complex organisms, *M abscessus* subsp *abscessus* and subsp *bolletii* are notable for resistance to multiple antibiotic agents, including inducible resistance to macrolides, coded by an erythromycin methylase gene.

Adenitis and SSTI

The preferred approach to the diagnosis of NTM adenitis is excision of the affected node, because incision and drainage can be complicated by fistula formation. Pathologic examination of affected tissue often reveals AFB with caseating or noncaseating granulomas. However, staining and pathology studies do not distinguish between disease due to NTM and *M tuberculosis*. In a 10-year review of NTM cases, the greatest diagnostic yield was observed with polymerase chain reaction testing of lymph node material (91.3% sensitivity), followed by culture (64.8% sensitivity) and microscopy for AFB (30.3% sensitivity). (20)

Pulmonary Disease

The US Cystic Fibrosis Foundation and the European Cystic Fibrosis Society, along with the Infectious Diseases Society of America and the American Thoracic Society, have developed recommendations for the diagnosis and treatment of NTM pneumonia. (10)(74) In contrast to *M tuberculosis*, the isolation of NTM from a nonsterile specimen (nasopharyngeal or gastric aspirate) may not imply respiratory disease and should be interpreted within a broader clinical context. The diagnosis of NTM-associated pulmonary disease requires clinical, radiologic, and microbiological evidence indicative of (or consistent with) NTM infection. Alternative diagnoses that could account for these findings should be excluded. For adults and older children, multiple (≥3) early morning sputum samples should be obtained for NTM culture. This approach improves the specificity and sensitivity of culture results. Because airway NTM colonization is common in children with CF, 2 positive sputum sample culture results are generally required to establish a diagnosis. Alternatively, culture of bronchoalveolar lavage fluid and induced sputum samples can be used to establish a diagnosis. In making the diagnosis of NTM-associated lung disease, the species of the isolated organisms should be taken into account because some species are unlikely to cause lung disease and more likely represent contamination.

TABLE 4. **Microbiological Tools for the Diagnosis of NTM Infection**

TOOL	UTILITY	COMMENTS
AFB smear	Rapid identification of mycobacteria in the specimen	AFB staining cannot distinguish among NTM species or between NTM species and *Mycobacterium tuberculosis*
Mycobacterial culture	Obtain an isolate for subsequent identification and possible susceptibility testing	Culture remains the gold standard for laboratory confirmation of NTM and is required for genotypic identification and drug susceptibility tests
DNA probes	Rapid identification/commercially available	Available for only certain species; cross-reactivity may occur
MALDI-TOF	Identification of organism	Accurate, rapid, and cost-effective system for identification of NTM species; discrimination power largely depends on the quality of the databases and cannot accurately differentiate *Mycobacterium abscessus* complex to the subspecies level
Gene sequencing (eg, 16S)	Identification of organisms to the species level	Multiple gene sequencing (*erm*, 23S rRNA, *hsp65*, and *rpoB*) can discriminate species

AFB=acid-fast bacillus; MALDI-TOF=matrix-assisted laser desorption/ionization–time of flight; NTM=nontuberculous mycobacteria.

Disseminated Disease

The diagnosis of disseminated disease is based on a positive AFB blood culture using bottles specifically intended for mycobacteria isolation. Bacteremia may be intermittent, so multiple cultures should be obtained. Cultures of other sites, including bone marrow and lymph nodes, may also be beneficial in making a diagnosis.

TREATMENT

The Infectious Diseases Society of America and the American Thoracic Society guidelines provide specific recommendations for the treatment of NTM infections. (10)(74) The Clinical and Laboratory Standards Institute has established standardized testing methods and cutoff values for susceptibility testing that can be used for RGM and SGM. This method allows for detection of macrolide resistance for certain NTM species (eg, MAC, *M abscessus,* and *M chelonae*) and rifampin resistance in *M kansasii,* which is invaluable for devising treatment regimens. Susceptibility testing can also be used to monitor for increasing resistance during antimicrobial drug therapy and for recurrent disease. Nonetheless, the value of in vitro testing is significantly limited by the lack of known cutoff values for certain species of NTM (especially fastidious organisms) and the clear lack of correlation between susceptibility results and clinical response. (10)

Lymphadenitis

The treatment of choice for NTM lymphadenitis is generally considered to be complete surgical excision of the infected lymph node. This recommendation, however, is based on somewhat limited data. The largest prospective study to date was a multicenter randomized controlled trial that compared surgical excision with antibiotic drug therapy in 100 children with NTM adenitis. A significantly higher success rate was found for surgical excision (96%) compared with antibiotic drug therapy (66%), although several methodological issues with this study exist. (28)(63) A meta-analysis conducted in 2015, which included almost 2,000 children, provides further support for the superiority of complete surgical excision compared with medical therapy, with cure rates of 98% and 73%, respectively. (75) Interestingly, watchful waiting alone was associated with a cure rate of 70.4%, which was not significantly different from medical therapy. Of note, facial nerve palsy occurred in approximately 10% of children who underwent surgical excision, with 2% of these cases being permanent. Furthermore, incomplete surgical excision was frequently associated with fistula formation.

Medical therapy may be used in children for whom surgical options are limited due to anatomical considerations (ie, close proximity of an infected lymph node to the facial nerve). Antimycobacterial regimens typically use more than 1 agent to prevent the emergence of resistance. Most cases (70%–90%) of NTM lymphadenitis in the United States are secondary to MAC (20), and *M scrofulaceum* accounts for much of the remaining disease. MAC adenitis has traditionally been treated with a macrolide (azithromycin or clarithromycin) combined with either rifabutin/rifampin or ethambutol. (76)(77) Compared with clarithromycin (7.5–15.0 mg/kg per dose orally twice daily; maximum dose, 500 mg), azithromycin has the advantage of once-daily dosing (10-mg/kg dose; maximum, 500 mg). For lymphadenitis caused by non-MAC species of NTM, therapy regimens should be tailored to historical data until results of susceptibility testing are available. The optimal duration of therapy is not known, but patients are often treated for a minimum of 12 weeks. (28) Because treatment failures with medical therapy are not infrequent, the clinician should always be alert to the possibility of drug resistance.

Skin and Soft Tissue Infections. A combination of surgery and lengthy medical treatment is usually required for the treatment of NTM-associated SSTIs. Medical therapy should be directed at the specific NTM species isolated. *M abscessus* infections are often difficult to treat secondary to drug resistance. Depending on the subspecies, clarithromycin, amikacin, and tigecycline have been demonstrated to have excellent in vitro activity against *M abscessus.* Suggested treatment includes a combination of macrolide, amikacin, and cefoxitin/imipenem in conjunction with surgical debridement. At least 4 months of antibiotic drug therapy with at least 2 weeks of intravenous therapy is recommended. (10)(20) Species-specific treatment considerations are provided in Table 5 for RGM infections.

Pulmonary Disease. Due to issues of drug resistance and toxicities, treatment of NTM pulmonary infection should be done in consultation with an infectious diseases specialist with expertise in this area. *M abscessus* complex lung disease requires an individualized treatment approach based on drug susceptibility test results. (74) Adjunctive surgery, including lobectomy, may be necessary to contain pulmonary disease. Treatment recommendations consist of an oral macrolide with 2 parenteral agents for several months. Parenteral choices include amikacin, cefoxitin, imipenem, and tigecycline. This is followed by a continuation phase of therapy, which consists of 2 to 3 oral

TABLE 5. **Species-Specific Treatment Considerations**

RGM	RESISTANCE PATTERNS	TREATMENT CONSIDERATIONS
Mycobacterium abscessus complex	• Subspecies dependent • Frequently resistant to clarithromycin	• Combination therapy with parenteral agents plus ≥1 oral agents have often been used in severe disease • Consider linezolid as a part of combination therapy • Clofazimine as a possible oral agent
Mycobacterium chelonae	• Uniformly resistant to cefoxitin	• Demonstrates frequent susceptibility to clarithromycin and linezolid • Intermediate susceptibility to imipenem, amikacin
Mycobacterium fortuitum	• Can also be resistant to macrolides • Generally less resistant to antimicrobial agents than other RGM • Considered easier to treat than other RGM	• Demonstrates frequent susceptibility to amikacin, ciprofloxacin, sulfonamides, and imipenem

RGM=rapidly growing mycobacteria.

drugs. The total suggested duration of therapy is 1 year after the development of negative sputum cultures. (10) The emergence of macrolide resistance in certain *M abscessus* subspecies complicates the management of these patients. Recently, there has been increased interest in the use of clofazimine as an oral agent to treat pulmonary NTM. (78) Unfortunately, patients with previous structural or immunologic derangement (ie, CF, AIDS) may fail to fully respond to this therapy. Surveillance for the emergence of increasing antimicrobial drug resistance and drug toxicity is indicated.

Disseminated Disease. Treatment of disseminated MAC disease should include antimicrobial management along with optimization of immune status. Initial treatment of disseminated MAC disease should consist of at least 2 or more antimycobacterial drugs to which the isolate is or is likely susceptible. (10)(79) The preferred first agent for MAC treatment is a macrolide (azithromycin or clarithromycin). The recommended second drug is ethambutol. (10)(79) Some clinicians add rifabutin as a third drug. For disseminated MAC disease, testing for macrolide susceptibility should be considered for all isolates, especially in patients who have persistent disease despite macrolide therapy or who develop disease while receiving macrolide prophylaxis. Without immune reconstitution, patients will require lifelong chronic maintenance therapy. (10) Primary prophylaxis (ie, before the advent of disease) with a macrolide should be given in children with severe immunosuppression secondary to advanced HIV infection, according to age-specific $CD4^+$ T-cell counts. Recommended macrolide primary prophylaxis doses are as follows: clarithromycin 7.5 mg/kg body weight (maximum, 500 mg) by mouth orally twice daily, or azithromycin 20 mg/kg body weight (maximum, 1,200 mg) orally once weekly. Treatment of catheter-associated infections has not been standardized. Most recommendations include removal of the affected catheter along with a course of antimycobacterial therapy directed at the specific species involved. (57)

Summary

- Based on strong evidence from independent gold standard studies of independent populations, nontuberculous mycobacteria (NTM) disease is acquired from environmental exposures and affects both immunocompetent and immunocompromised children. (15)(20)
- Based on strong evidence from independent gold standard studies of independent populations, rapidly growing NTM, which are resistant to a variety of antimycobacterial agents, have become an important cause of skin and soft tissue infections, and outbreaks of disease have been reported in association with medical tourism. Likewise, pulmonary infections due to resistant NTM have become increasingly problematic for patients with CF. (2)(34)(37)
- Based on strong evidence from independent gold standard studies of independent populations, advances in molecular biology have led to improved diagnostics, which provide for a timelier diagnosis and allow for differentiation of organisms at the species and subspecies levels. Depending on the host and type of disease, this differentiation may be important in guiding initial therapy before susceptibilities are available. (10)(72)(74)
- Based on strong evidence from independent gold standard studies of independent populations, treatment of NTM-associated disease is site specific and should also take into account the immune status of the host and organism susceptibility testing results. (2)(10)(75)

References for this article are at http://pedsinreview.aappublications.org/content/40/4/179.

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1. A 2-year-old otherwise healthy boy is brought to the clinic with a 3-week history of slowly progressive left neck swelling. The parents report that he has been afebrile and had normal appetite and activity. His vaccinations are up-to-date. He was born in the United States and his growth and development up to this point have been normal. The paternal grandmother is originally from India but has lived with them for the past 3 years. There are no recent sick contacts or travel outside the United States. Three months ago, he visited his cousin's house with his parents. The cousin has 2 older cats. He was seen in an urgent care center 1 week earlier and was prescribed oral cephalexin, which he has been taking with no improvement in the appearance of the swelling. On physical examination today he is nontoxic appearing, playful, and interactive. He is afebrile with normal vital signs. There is a swollen, firm, fluctuant, and minimally tender left anterior cervical lymph node with the overlying skin appearing thin and violaceous. The node measures approximately 2 cm. A small sinus tract appears to be forming in the center of the node. There is no other adenopathy appreciated and no hepatosplenomegaly. The rest of the physical examination is normal. Which of the following is the most likely diagnosis in this patient?
   A. Cat-scratch disease.
   B. Infectious mononucleosis.
   C. Lymphoma.
   D. Nontuberculous mycobacterium (NTM).
   E. Tuberculosis.
2. An 18-year-old girl presents to the emergency department with bilateral breast pain and left breast drainage. She had undergone bilateral breast reduction surgery in the Dominican Republic 5 weeks before presentation. Three weeks postoperatively she complained of fevers, chills, and purulent discharge from the left breast. At that time, the discharge was cultured by her primary care provider, and Gram-stain of the fluid showed gram-positive cocci in clusters. She was sent home on a 2-week course of oral trimethoprim-sulfamethoxazole. Four days before presentation she had an increase in her breast pain, wound dehiscence of the left breast, and temperatures to 103°F (39.4°C). Which of the following organisms is most likely to be the cause of her infection?
   A. *Mycobacterium abscessus*.
   B. *Mycobacterium haemophilum*.
   C. *Mycobacterium marinum*.
   D. *Mycobacterium tuberculosis*.
   E. *Mycobacterium ulcerans*.
3. The patient in the previous vignette underwent ultrasonography of the left breast that showed a 1.4-cm loculated fluid collection. You suspect an NTB to be the cause of her illness. Which of the following is the gold standard laboratory test for making the diagnosis of NTB in this patient?
   A. Acid-fast bacillus or fluorochrome staining of sputum.
   B. Interferon-γ release assay.
   C. Isolation of the organism in culture.
   D. Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) testing.
   E. Tuberculin skin testing.

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4. A 4-year-old girl is brought to the clinic with a 5-week history of a progressive, unilateral, nontender lymph node swelling on the right side of her neck. She was seen 2 weeks earlier, diagnosed as having cervical lymphadenitis, and prescribed a 10-day course of oral clindamycin, which she completed without improvement. Her parents deny any fevers, chills, weight loss, or cough. She has no known sick contacts and no international travel history. A complete blood cell count and erythrocyte sedimentation rate are obtained and they are both normal. NTM lymphadenitis is suspected. Which of the following is the next best step in management?

   A. Antimicrobial therapy against NTM.
   B. Blood culture for mycobacteria isolation.
   C. Incision and drainage of the node.
   D. Surgical excision of the node.
   E. Throat swab for culture.

5. A 15-year-old boy with a history of congenital human immunodeficiency virus (HIV) infection and herpes simples virus esophagitis 1 year earlier presents for routine follow-up. He reports increasing fatigue, poor appetite, and weight loss but denies fevers, diarrhea, cough, sore throat, or night sweats. On examination, his vital signs are within normal limits. He has lost 2 kg since his last visit 3 months earlier. On oropharyngeal examination he is noted to have oral thrush. The rest of his examination findings are normal. He admits that he is not always compliant with his antiretroviral therapy. His CD4 count is 44 cells/μL. In addition to close clinical monitoring and optimization of his antiretroviral therapy, the clinician decided to begin him on prophylaxis for *Mycobacterium avium* complex (MAC). Which of the following antimicrobial agents is recommended for primary MAC prophylaxis of patients with severe immunosuppression secondary to advanced HIV infection?

   A. Amikacin.
   B. Azithromycin.
   C. Doxycycline.
   D. Pyrazinamide.
   E. Rifampin.

Nontuberculous Mycobacterial Infections in Children

Jyotsna Bhattacharya, Sindhu Mohandas and David L. Goldman

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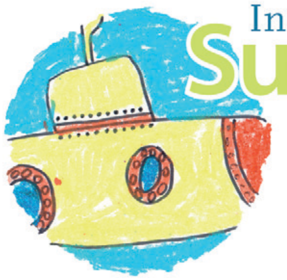

Index of Suspicion

1 Intermittent Fevers, Persistent Vomiting, and Lethargy in a 3-year-old Boy

Archana Balamohan, MD,* Lorry G. Rubin, MD,* Peter Assaad, MD,[†]
Stefan H.F. Hagmann, MD, MSc*

*Division of Pediatric Infectious Diseases and [†]Division of Pediatric Radiology, Steven and Alexandra Cohen Children's Medical Center/Northwell Health, New Hyde Park, NY; Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY

EDITOR'S NOTE

Last month, we thought globally, and *Index of Suspicion* included 4 cases of conditions that are more common outside of North America than they are within the United States. This month, 2 of the review articles focus on mycobacterial infections that can present anywhere in the world. Our cases include children with symptoms suggestive of mycobacterial infection, but some of these children ended up having different problems. Enjoy thinking through these cases!

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A 35-month-old boy with a history of speech and slight motor delay is transferred to our institution with a 1-month history of intermittent fever and a 2-week history of vomiting. During this time he was noted to have poor appetite and a change in personality progressing to lethargy and generalized weakness. In addition, he has been pointing to his head for the past few days, perhaps indicating headache. He is US-born and frequently travels to Guyana, where he has been residing for the past 4 months with his maternal family. Treatment in Guyana included a 7-day course of amoxicillin-clavulanate for presumed acute otitis media and a subsequent course of an unknown antibiotic for treatment of pharyngitis and suspected bacteremia. Computed tomography of his head performed 1 month after onset of symptoms revealed hydrocephalus, and he returned 1 day later to the United States for further medical care.

At initial presentation he is afebrile (100°F [37.8°C]) with a heart rate of 128 beats/min, respiratory rate of 20 breaths/min, blood pressure of 121/92 mm Hg, and oxygen saturation of 97% in room air. He appears malnourished (weight of 10 kg [<2nd percentile]) and is noted to have a normal-shaped head (head circumference, 50 cm [58th percentile]). He is irritable and listless at times. Cranial nerve examination results are normal, and he moves all his extremities equally. Nuchal rigidity is not appreciated. He demonstrates nasal flaring and suprasternal and subcostal retractions, but lung auscultation was normal. The remainder of the examination findings are normal.

AUTHOR DISCLOSURE Drs Balamohan, Rubin, Assaad, and Hagmann have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

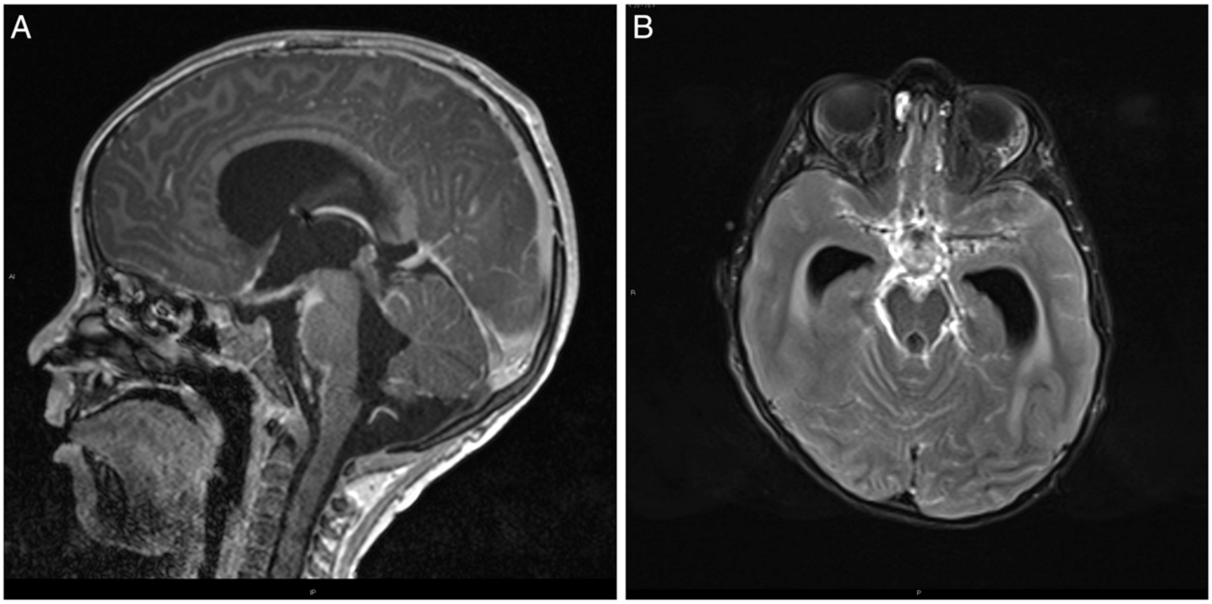

Figure 1. Magnetic resonance images of the patient's brain. A. Sagittal T1-weighted magnetization-prepared rapid gradient-echo postcontrast view demonstrating basal cistern and leptomeningeal enhancement. B. T2-weighted fluid-attenuated inversion recovery fat-saturated postcontrast view demonstrating leptomeningeal and cisternal enhancement involving the quadrigeminal and suprasellar cisterns.

Laboratory studies reveal a white blood cell count of 14,300/μL (14.3×10^9/L), hematocrit value of 39%, platelet count of 487×10^3/μL (487×10^9/L), serum sodium level of 131 mEq/L (131 mmol/L), and normal liver transaminase levels. Magnetic resonance imaging of the head shows dilatation of the lateral, third, and fourth ventricles without evidence of aqueduct obstruction. After contrast administration, marked basilar and leptomeningeal enhancement is evident (Fig 1).

DISCUSSION

Our patient had signs of increased intracranial pressure. He was emergently intubated and underwent right frontal ventriculostomy (opening pressure of >40 cm H_2O) and externalized ventricular drain placement. His ventricular cerebrospinal fluid (CSF) had 14 nucleated cells (28% segmented cells, 56% lymphocytes, 16% monocytes), 16 red blood cells, a glucose level of 44 mg/dL (2.44 mmol/L), and a protein level of 0.03 g/dL (0.32 g/L). The CSF Gram-stain and acid-fast bacillus (AFB) stain were negative, as was cryptococcal antigen. The CSF nucleic acid amplification (NAA) assay was negative for *Escherichia coli* K1, *Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae,* cytomegalovirus, enterovirus, herpes simplex viruses 1 and 2, human herpesvirus 6, human parechovirus, varicella-zoster virus, and *Cryptococcus neoformans*. In view of his subacute presentation with basilar meningitis and substantial time spent in a tuberculosis (TB)-endemic region, TB meningitis (TBM) was a likely diagnosis, and he was empirically started on 4-drug therapy (rifampin, isoniazid, pyrazinamide, and ethionamide), along with corticosteroid therapy. A chest radiograph was normal, and 3 sequential gastric aspirate samples tested negative for AFB by smear. Results of a TB skin test and TB interferon-γ release assay were negative. One of 2 separate CSF samples tested positive for *Mycobacterium tuberculosis* by an NAA assay. In addition, the CSF (after 17 days of incubation) and 1 of 3 sputum cultures (after 20 days of incubation) grew *M tuberculosis*, and the sensitivity testing indicated a pansensitive organism. Human immunodeficiency virus infection was ruled out. The externalized ventricular drain was converted to a ventriculoperitoneal shunt on the fourth hospital day. As the boy's appetite and energy level started to improve, he tolerated his anti-TB medication by mouth very well. After receiving a 2-week course of prednisolone (2 mg/kg daily), his corticosteroids were tapered over a 3-week period. He returned to his normal self and baseline activity level within 4 weeks of discharge. He has currently completed 4 months (of a planned 12-month course) of anti-TB therapy and remains well.

The Condition

TBM is the most debilitating and frequently fatal form of TB. (1) Although rare, occurring in less than 2% of all patients with TB, (2) it disproportionately affects young children. (1) Central nervous system TB is thought to arise from lymphohematogenous spread of tubercle bacilli during initial infection, where they form a caseous lesion in the brain, also known as the Rich focus. Tubercle bacilli are discharged from there into the subarachnoid space, resulting in inflammation that has a predilection for the base of the brain and may result in cranial nerve III, VI, and VII involvement. A thick and gelatinous exudate forms and can interfere with normal CSF flow, resulting in communicating hydrocephalus, and can extend along vessels into the cortex and lead to infarction. (3) Hence, on neuroimaging (computed tomography or magnetic resonance imaging), hydrocephalus and basilar meningeal enhancement are most commonly encountered. (3)(4)

Clinically, 3 stages of TBM have been described. In stage I, nonspecific constitutional symptoms, headache, (2) and personality change (3) are seen. Stage II is manifested by symptoms of meningitis (nuchal rigidity, vomiting, seizures), cranial nerve abnormalities, and long tract signs. Stage III is characterized by coma, hemiplegia or paraplegia, decerebrate or decorticate posturing, progressive vital sign changes, and eventual death. (2)(4)

Diagnosis

The diagnosis of TBM is challenging and often requires a high index of suspicion in a child with a subacute presentation of meningitis, with or without hydrocephalus. During the clinical evaluation of a child with suspected TBM, alternative infectious causes of bacterial, viral, fungal, and protozoal origin, as well as noninfectious causes (eg, systemic vasculitic syndromes, hemorrhage, or leukemic infiltrates) need to be considered as possible differential diagnoses. In this context, the review of the epidemiologic history is crucial to identify patients who have either traveled to TB-endemic regions or been exposed to ill contacts with TB.

Analysis of CSF usually demonstrates lymphocytic predominant pleocytosis, hypoglycorrhea, and an elevated protein level. However, ventricular CSF may be normal or show only subtle evidence of inflammation compared with lumbar CSF. (3) Tuberculin skin testing results are frequently nonreactive (>45% of cases). (3)(4) The diagnostic modality of choice is microbiological confirmation, although this can be challenging. Staining with AFB and mycobacterial culture of CSF is positive in less than 10% and approximately 35% of patients, respectively. (5) The yield can be increased if a large volume of CSF (≥10 mL) is cultured. NAA testing of CSF, although an off-label use of the test, may be helpful in establishing the diagnosis. A positive result can be used as evidence of TBM because a false-positive result is unlikely. However, false-negative results are common, and a negative result does not exclude TBM. (6)

Management

TBM has the greatest morbidity and mortality rates of all *M tuberculosis* infections, with the rates directly correlated to the stage at which effective therapy is initiated. (4) Therefore, children with clinical, laboratory, or radiologic findings suspicious of TBM and the presence of epidemiologic risk factors should be empirically started on anti-TB treatment. Treatment for TBM consists of 4 drugs initially (rifampin, isoniazid, pyrazinamide, and ethionamide or streptomycin); ethionamide is preferred over ethambutol due to its increased blood-brain barrier penetration. (1) Treatment with pyrazinamide and ethionamide is usually stopped after 2 months (provided drug resistance has been ruled out by susceptibility testing), and isoniazid and rifampin are continued for 9 to 12 months. Corticosteroids (eg, 1–2 mg/kg per day of prednisone) for the first month of treatment followed by a taper has been associated with a reduced risk of mortality (7)(8) and improved intellectual outcome. (8) Ventriculoperitoneal shunt placement is often warranted to relieve intracranial pressure, prevent herniation, and improve neurologic deficits. (3)(4)

Lessons for the Clinician

- In tuberculosis (TB) low-endemicity regions such as the United States, travel and exposure history are key to considering the diagnosis of TB in a child.
- The symptoms of TB meningitis (TBM) are often initially subtle and develop subacutely; hence, a high index of suspicion is required.
- Cranial computed tomography and, in particular, magnetic resonance imaging may increase suspicion of TBM by demonstration of basilar enhancement with noncommunicating hydrocephalus.
- The diagnostic modality of choice is microbiological confirmation of mycobacterial infection from cerebrospinal fluid. The diagnostic yield can be improved by obtaining high-volume cerebrospinal fluid samples (≥10 mL) and using nucleic acid amplification–based tests.
- Therapy for TBM consisting of a 4-drug regimen and corticosteroids should be started empirically due to the high degree of mortality and morbidity while the diagnosis is being confirmed.

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Case 1: Intermittent Fevers, Persistent Vomiting, and Lethargy in a 3-year-old Boy

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Index of Suspicion

2 Lethargy and Ataxia in a 3-year-old Girl

Patrick Gavigan, MD,*†‡ Nicholas D. Hysmith, MD,*‡ Bindiya Bagga, MD*‡

*University of Tennessee Health Science Center, Memphis, TN
†St. Jude Children's Research Hospital, Memphis, TN
‡Le Bonheur Children's Hospital, Memphis, TN

PRESENTATION

A 3-year-old previously healthy girl presents with progressive lethargy and ataxia over the past 7 days. Her mother reports that she has been increasingly sleepy and difficult to awaken, and over the past 3 days has had increasingly unsteady gait. In addition, she has had fatigue, cough, and decreased oral intake for the past 2 to 3 weeks. Her mother denies any fevers, weight loss, travel, or unusual exposures. She and her family are from an urban area in the Southeastern United States.

On physical examination she is afebrile without tachypnea or tachycardia. She is ill-appearing and sleepy but arouses with stimulation and follows simple commands. She has right-sided ptosis, right-sided facial weakness, and right-sided arm and leg weakness. Deep tendon reflexes are present in all extremities. Cerebrospinal fluid (CSF) analysis shows a white blood cell count of 68/μL (0.07×10^9/L) with 33% neutrophils, 60% lymphocytes, and 7% monocytes; a red blood cell count of 42/μL (0.000042×10^{12}/L); a glucose level of 26 mg/dL (1.4 mmol/L); and a protein level of 115 mg/dL (1.15 g/L). The remainder of the physical examination and basic laboratory values, including serum electrolytes, renal and liver function, and complete blood cell count, are within normal limits, although the C-reactive protein level is elevated at 10.8 mg/L (102.9 nmol/L) (reference range, <9.0 mg/L [<85.7 nmol/L]).

A computed tomographic (CT) scan of the head shows tetraventricular hydrocephalus (Fig 1). Empirical ceftriaxone, vancomycin, doxycycline, and acyclovir are started, without any clinical improvement. A brain magnetic resonance image demonstrates basilar meningitis. Results of CSF testing with bacterial culture, fungal culture, acid-fast bacilli (AFB) stain and culture, and herpes simpex virus polymerase chain reaction are negative. Results of additional evaluations with tuberculosis (TB) skin testing, blood culture, Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus testing are negative. Chest radiography reveals left upper lobe atelectasis. Despite a negative exposure history, negative TB skin test result, and inconclusive initial chest radiograph, empirical therapy for TB was started on day 2 of hospitalization due to clinical deterioration. Chest CT (Fig 2) leads to additional testing that reveals the diagnosis.

AUTHOR DISCLOSURE Drs Gavigan, Hysmith, and Bagga have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

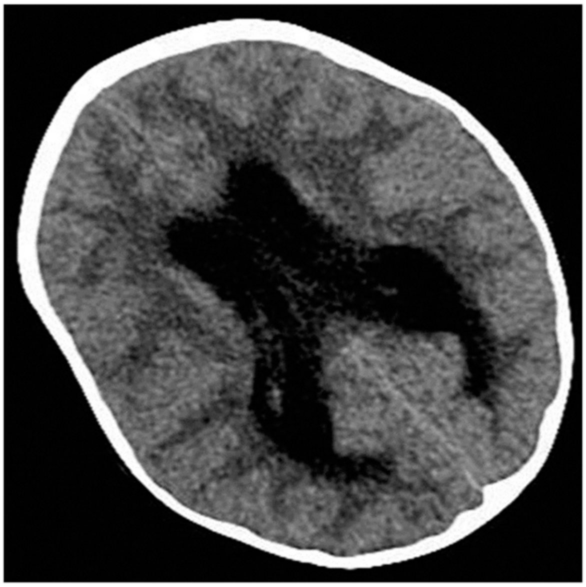

Figure 1. Computed tomographic scan of the head of the patient demonstrating tetraventricular hydrocephalus.

DISCUSSION

Clinical Course

On further history, the mother revealed that the patient's aunt was treated for active TB approximately 1 year earlier and had been noncompliant with her medications. In addition, whereas the patient's siblings had received prophylactic therapy at that time, the patient had not. Given the subtle chest radiography findings, a chest CT scan was obtained, and it demonstrated a cavitary lesion in the left upper lobe. Subsequent gastric aspirate culture was positive for *Mycobacterium tuberculosis,* confirming the diagnosis of TB.

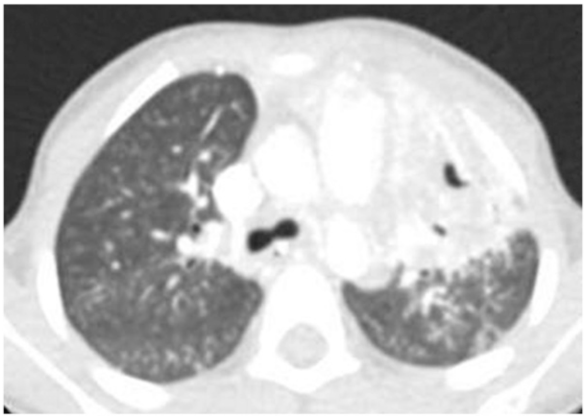

Figure 2. Computed tomographic scan of the chest of the patient demonstrating a left upper lobe cavitary lesion.

After starting rifampin, isoniazid, pyrazinamide, moxifloxacin, and prednisone for TB meningitis, she began to demonstrate clinical improvement. Her mental status and neurologic examination findings improved; however, she did require intensive rehabilitation, as well as a ventriculoperitoneal shunt due to persistent hydrocephalus. She was eventually discharged to finish her course of medication through direct observed therapy by the health department.

Epidemiology and Pathogenesis

Central nervous system (CNS) involvement of TB is rare, occurring in less than 2% of cases, with meningitis representing approximately 1%. However, it is most common in children, especially those younger than 2 years. (1) Although the overall annual rates of TB in the United States have decreased to approximately 3 per 100,000, the morbidity and mortality associated with TB meningitis remain high. (1)(2) Involvement of the CNS results from direct extension and establishment of infection in the brain and meninges during periods of bacillemia that occur with primary infection or late reactivation. Small caseating granulomas form in the brain tissue, and meningitis occurs when these granulomas rupture, releasing bacteria into the subarachnoid or ventricular spaces. (1)(3)

Clinical Presentation

Patients with TB meningitis can present with any number of nonspecific symptoms but typically develop a subacute clinical course that progresses through 3 stages. Stage I typically lasts 1 to 3 weeks and consists of an initial prodromal phase of malaise, headache, and low-grade fever. Patients in stage I of the disease have no neurologic deficits or hydrocephalus. Stage II is characterized by meningeal inflammation and cranial nerve palsies. These patients often have focal neurologic deficits, severe headaches, vomiting, lethargy, and confusion. The exact duration of stage II is unclear and is determined by the underlying host immunity and the disease burden. Finally, stage III involves worsening mental status, with stupor, coma, seizures, and hemiparesis, due to progressive hydrocephalus and vasculitis. (1)(2)(3) Weight loss and night sweats, frequently seen in patients with pulmonary TB, are present in only 25% of patients with TB meningitis. Prognosis is often directly related to early initiation of anti-TB therapy. Unfortunately, as many as 90% of children with TB meningitis are not identified until stage II or III, when they develop focal neurologic signs. (2)(4)

Diagnosis

Definitive diagnosis is established by AFB stain and culture of CSF, but this is challenging given the low sensitivity of

CSF AFB stain and culture. (2)(4) Similarly, TB skin testing and interferon-γ release assays are unreliable in the diagnosis of CNS TB, and they are positive in only 33% of cases. (1)(2)(4) Nucleic acid amplification tests on CSF are not readily available and are limited by their varying sensitivity and specificity. (5)

With no reliable test available for TB meningitis, clinicians must rely on history and clinical, laboratory, and radiographic findings. In a young child, TB meningitis is a consequence of primary infection and, thus, requires exposure to active TB. Accordingly, a history of any patient exposure to confirmed or potential TB cases is important. However, a contact case is identified in only 50% to 70% of patients with TB meningitis, and there is often a significant delay in identifying this source. Abnormalities in CSF are one of the most consistent findings in patients with TB meningitis. The characteristic lymphocytic pleocytosis with extremely elevated protein and decreased glucose levels is seen in approximately 80% of patients. Imaging to look for pulmonary disease and evaluate for CNS disease is also valuable in making the diagnosis. The most common radiographic findings of TB meningitis include abnormal chest radiographs (90% of patients) and hydrocephalus (80% of patients). (1)(4) Less commonly, basilar meningitis and infarcts are seen on head imaging. (1)(2)(4)

Management

Anti-TB therapy typically consists of rifampin, isoniazid, pyrazinamide, and ethambutol. (1)(3) In cases of meningitis, an aminoglycoside, ethionamide, or moxifloxacin should be substituted for ethambutol given their superior CSF penetration. (5)(6) Treatment with anti-TB therapy is recommended for 9 to 12 months. The 4 medications are administered for the first 2 months, and then treatment is completed with rifampin and isoniazid for an additional 7 to 10 months. In addition to antimicrobials, corticosteroids are also recommended for 4 to 6 weeks, followed by a taper. (1)(5) Corticosteroids have been associated with decreased mortality and neurologic sequelae; however, ventriculoperitoneal shunting is frequently required to relieve hydrocephalus.

Lessons for the Clinician

- Nonspecific symptoms, rarity of occurrence, and difficulties with history can lead to delays in diagnosis and initiation of appropriate therapy in patients with tuberculosis (TB) meningitis.
- TB should be suspected in patients with subacute aseptic meningitis even in the absence of typical risk factors (travel to or residence in an endemic country, known exposure, weight loss, chronic cough).
- Cerebrospinal fluid (CSF) culture for *Mycobacterium tuberculosis* and TB skin testing are often unreliable for diagnosis of TB meningitis owing to poor sensitivity.
- TB meningitis is most commonly associated with lymphocytic pleocytosis, an elevated protein level, and a low glucose level on CSF analysis and with hydrocephalus on head imaging.
- In individuals with suspected TB meningitis, empirical TB therapy should be initiated, even in the absence of definitive diagnosis, to reduce morbidity and mortality associated with the disease.
- An attempt should be made to find the primary pulmonary focus in children with suspected extrapulmonary TB.

References for this article are at http://pedsinreview.aappublications.org/content/40/4/194.

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Case 2: Lethargy and Ataxia in a 3-year-old Girl

Patrick Gavigan, Nicholas D. Hysmith and Bindiya Bagga

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3 Two Preschoolers with Fever

Shraddha Mittal, MD,*† Lauren Marlowe, MD,*† Dustin Elliott, MD,*†
Deana Gifford, MD,*† Kristen Ritenour, MD,*† Howard Topol, MD*†

**Children's Hospital of Philadelphia, †CHOP Inpatient Pediatrics at Virtua, Voorhees, NJ*

CASE 1

A 15-month-old Boy with Fever, Refusal to Bear Weight, and Small Foot Lesions

Presentation

A 15-month-old boy presents to the emergency department in May with a 3-day history of fever, irritability, poor oral intake, and refusal to bear weight. He has no history of cough, vomiting, diarrhea, or rash other than a lesion on the sole of his left foot, where his mother reports there was a possible insect bite 1 week earlier. He was previously healthy, and his immunizations are up to date. He lives in a rural area of southern New Jersey. The family denies recent travel or ingestion of raw foods or milk. He had visited a farm 2 weeks earlier but denies direct contact with farm animals. He has had contact with a 2-year-old cat but denies bites or scratches.

On examination he is ill appearing. Vital signs reveal a temperature of 103.5°F (39.7°C) and tachycardia. He is irritable but does not have meningismus. His abdominal examination findings are normal. He has no appreciable lymphadenopathy. On extremity examination his strength is normal. He has two 2-mm, erythematous, raised, tender papules on the plantar aspect of his left foot, but otherwise no specific tenderness to palpation or swelling along his lower extremities. Due to fever and irritability, he underwent a full sepsis evaluation, including lumbar puncture, blood culture, and urine culture. Initial cerebrospinal fluid cell count was normal. His laboratory values are notable for a white blood cell (WBC) count of $15,700 \times 10^3/\mu L$ ($15.7 \times 10^9/L$), with 60% neutrophils, 31% lymphocytes, and 6% bands; C-reactive protein (CRP), 115 mg/L (1,095 nmol/L); and erythrocyte sedimentation rate, 31 mm/hr. He receives a normal saline bolus and is admitted to the inpatient pediatrics ward without empirical antibiotics.

DISCUSSION

While hospitalized, he continues to have daily fever, with a temperature ranging from 101.8°F to 104.5°F (38.8°C –40.3°C). His irritability and oral intake improve, but he still refuses to bear weight. His WBC count peaks at $24,000/\mu L$ ($24.0 \times 10^9/L$), but his CRP level and ESR trend downward. His cultures from blood, urine, and CSF samples are negative. He tests positive for

AUTHOR DISCLOSURE Drs Mittal, Marlowe, Elliott, Gifford, Ritenour, and Topol have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

human rhinovirus/enterovirus by polymerase chain reaction (PCR) of respiratory secretions. He tests negative for Epstein-Barr virus, cytomegalovirus, and *Bartonella* by serologic testing. Abdominal ultrasonography is performed to evaluate nonspecific tenderness on examination and reveals mild splenomegaly (9.4 cm) and trace perihepatic fluid.

Owing to his persistent refusal to bear weight on the left lower extremity, imaging is obtained. He has normal ultrasonography findings of the left hip and normal plain radiography findings of the left femur, tibia, and fibula. Magnetic resonance imaging findings of the left lower extremity are negative other than an incidental finding of mild left inguinal lymphadenitis. This soon becomes clinically apparent, and he is started on clindamycin intravenously.

Through the hospitalization, his examination shows continued evolution of foot lesions. The 2 papules progress into coalescing vesiculopustules, the larger one measuring 7.5 mm, surrounded by pinpoint vesicles (Fig 1). Serial cultures are obtained and are pending. Owing to persistent fever, he is transferred to a tertiary care pediatric hospital on day 4 for a pediatric infectious disease consultation, where results of an extended viral PCR panel of a stool sample are negative. He also tests negative for cytomegalovirus, human herpesvirus 6, adenovirus, enterovirus, and parvovirus by PCR of a blood sample. Despite persistent fever, his behavior and disposition improve, and he is discharged with a diagnosis of presumed viral infection.

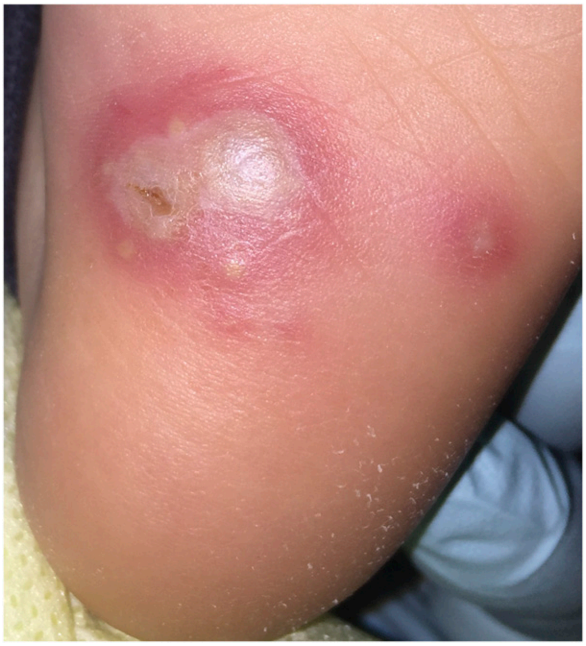

Figure 1. Case 1: papulopustular lesions on the left foot.

After discharge, the second wound culture grows a gram-negative coccobacilli suspicious for *Francisella tularensis*, which is confirmed by the state laboratory using PCR. He is treated with ciprofloxacin. His fever resolves, and he makes a full recovery.

CASE 2

A 4-year-old with Fever, Cervical Lymphadenopathy, and Pulmonary Nodules

Presentation

A previously healthy 4-year-old girl presents in June with a 2-week history of persistent high temperatures up to 102.9°F (39.4°C) and worsening right cervical lymphadenopathy. Her mother had removed a tick from her scalp 2 days before the onset of her symptoms, and she has developed an enlarging pustuloulcerative lesion at that site.

She denies cough, weight loss, and night sweats. There is no history of international travel, exposure to tuberculosis, bites or scratches by kittens, or other animal exposure. She has no significant medical or surgical history, and her family and social history are unremarkable.

Since the onset of fever she has received 2 days of amoxicillin for possible otitis media, followed by 2 days of intravenous clindamycin for suspected cellulitis, and she has completed 9 of 14 days of amoxicillin/clavulanic acid for suspected Lyme disease.

Despite this, her fever and scalp lesion have persisted and her neck mass has increased considerably in size. She is seen at an outside emergency department, diagnosed as having cervical adenitis, and admitted to our community hospital on intravenous clindamycin.

Physical examination reveals a temperature of 101.5°F (38.6°C) but otherwise stable vital signs. She appears well but seems to be in pain from her neck mass. Examination of the scalp reveals a 1 × 1-cm shallow ulcer covered with dried pus and with surrounding erythema (Fig 2). She has a large 5 × 8-cm mass in her right neck extending from behind the ear to the lower neck; it is erythematous, multilobulated, firm, and tender, with mild fluctuation (Fig 3). Her neck movements are limited secondary to pain. The remainder of the examination findings are normal. Specifically, there are no other enlarged lymph nodes, her chest is clear, and there is no hepatosplenomegaly.

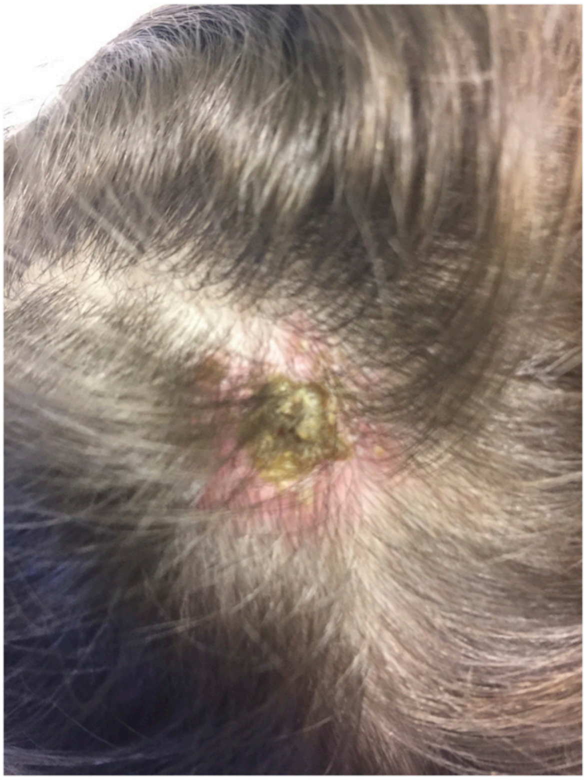

Figure 2. Case 2: pustular ulcerative lesion on the right scalp at the site of a tick bite.

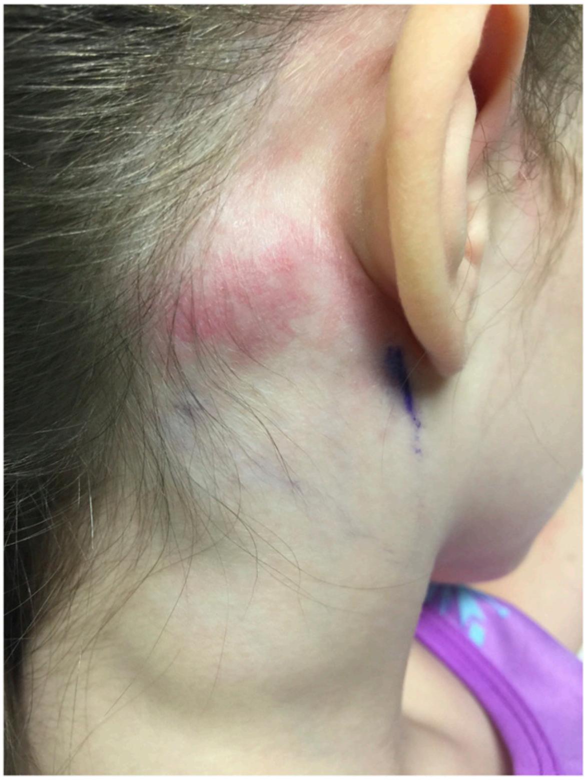

Figure 3. Case 2: 5 × 8-cm ipsilateral, right cervical and postauricular lymphadenitis.

DISCUSSION

A complete blood cell count shows a high WBC count at 17,300/μL (17.3 × 10^9/L), with 71% neutrophils, 20% lymphocytes, and 7% monocytes. She has an elevated CRP level of 92 mg/L (876 mmol/L) and an ESR of 76 mm/hr. A computed tomographic scan of her neck reveals multiple phlegmonous lymph nodes as well as 2 small (3- to 4-mm) pulmonary nodules in the lung apices (Fig 4). Chest radiography is negative, with no apparent nodules and no hilar lymphadenopathy.

Ulceroglandular tularemia is suspected based on the course of her illness over the preceding 2 weeks with a nonhealing scalp lesion after tick bite, persistent fever, worsening regional suppurative lymphadenopathy, and poor response to clindamycin and amoxicillin/clavulanic acid. Pulmonary nodules were thought to have resulted from transient bacteremia and miliary spread to the lungs.

Blood culture, wound culture, and tularemia antibodies are sent for testing. The laboratory and the Department of Health are notified about the possibility of tularemia, and the patient is started on intravenous gentamicin. *Bartonella* titers are also sent for testing, and a purified protein derivative test is performed.

Her fever resolved within 2 days, but she required incision and drainage for suppurating lymph nodes. She was discharged 3 days later on oral ciprofloxacin.

Tularemia antibody titers were consistent with a diagnosis of tularemia (1:2,560; reference range, <1:20). Blood and wound cultures were negative. Results of purified protein derivative and *Bartonella* testing were also negative. Lymph node pathologic analysis showed epithelioid cell granulomas and caseous necrosis consistent with tularemia. Lymph node cultures including acid-fast bacillus were negative.

THE CONDITION

Tularemia (deerfly fever, rabbit fever) is caused by *F tularensis*, an aerobic, fastidious, gram-negative coccobacillus. The bacterium was first discovered in 1906 in Tulare County in California and was named *Bacterium tularense* after the county. Human disease (deerfly fever) was first described in 1911, but it was not until 1924 that a US public health physician, Dr Edward Francis, linked the bacterium to the disease. The bacterium was renamed *Francisella tularensis* in his honor. There are 4 known subspecies, with different levels of pathogenicity and presentations. The subspecies tularensis, found in the United States, is one of the most

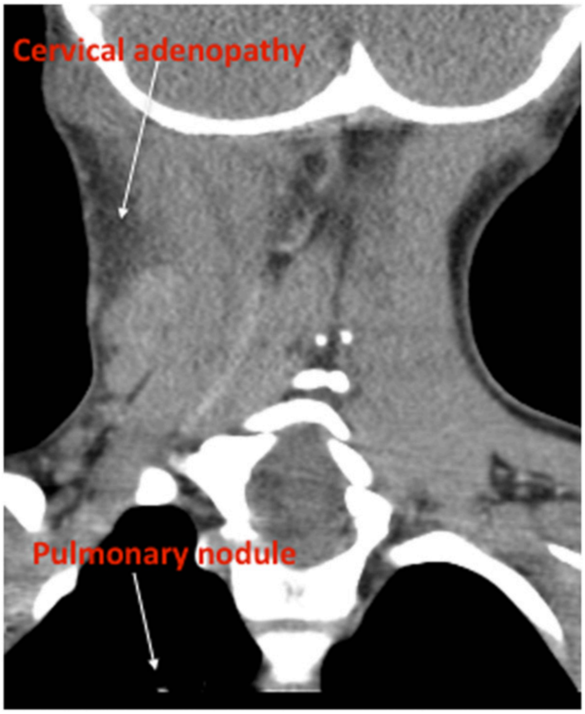

Figure 4. Case 2: computed tomographic scan of the neck showing extensive suppurative right cervical adenitis and a pulmonary nodule in the apex of the right lung.

pathogenic organisms, with potential for use as a bioterrorism agent.

Tularemia affects many animals, including rabbits, squirrels, muskrats, beavers, and voles, which act as a reservoir. Transmission can occur from animal contact (handling, ingestion, bite), from arthropod bites, or through contaminated water and soil; however, insect bite is the most common mode of transmission in children. Ticks (wood tick, dog tick, lone star tick) are the most common vector in most of the United States, but deerflies, horseflies, mosquitoes, fleas, and lice can also transmit the disease. Transovarian transmission in ticks allows for human transmission without the need for an infected-animal reservoir. Person-to-person spread does not occur.

Tularemia is rare in the United States, with approximately 100 to 200 reported cases per year since the early 1990s. Most cases occur in the south-central states, but there has been a recent shift to the north.

Tularemia is rare in New Jersey, with only 8 reported cases between 2001 and 2015, with the greatest incidence in June and July. However, our 2 cases represent a significant surge, with 4 reported cases in the first 8 months in 2016. The NJ Department of Health speculates that the increased incidence in New Jersey is a result of local infected rabbit populations, which are spreading the infection to ticks. Our first case may have been from the child injuring the sole of his foot from the remains of an infected rabbit. The second case likely occurred from a tick bite on the scalp.

The incubation period for tularemia is 3 to 5 days, with a range of 1 to 21 days. Once inoculated into the skin, the organism multiplies at the site of inoculation, spreads to regional lymph nodes, and may spread further via the lymphohematogenous route.

Childhood tularemia most commonly presents in children aged 5 to 10 years, with glandular tularemia marked by fever and lymphadenitis, mostly in the cervical or occipital region. The second most common presentation is ulceroglandular, which in addition to the symptoms in the glandular form presents with an erythematous papuloulcerative lesion with a central eschar at the site of the bite. Hematogenous spread can cause secondary pneumonia or miliary disease, which can be asymptomatic. Other rare forms include primary pneumonic, typhoidal (fever), oculoglandular (conjunctivitis), and oropharyngeal disease.

Childhood tularemia often presents as lymph node suppuration, with 20% of children needing incision and drainage. Rare presentations include sepsis, renal failure, rhabdomyolysis, mastoiditis, meningitis, empyema, hepatitis, osteomyelitis, peritonitis, endocarditis, and pericarditis.

Presumptive diagnosis is by detection of elevated serum antibody titers to *F tularensis* antigen (without documented minimum 4-fold change) or detection of *F tularensis* in a clinical specimen by fluorescent assay.

Confirmation requires isolation of *F tularensis*. Isolates are confirmed by PCR assays available from state laboratories. PCR can also be used on biological specimens but is not as sensitive. A 4-fold change in serum antibody titers can also be used to confirm the diagnosis.

Recommended treatments for children include intravenous gentamicin for 7 days or oral ciprofloxacin for 10 to 14 days for moderate disease, with longer therapies for serious infection.

The differential diagnosis of ulceroglandular tularemia includes rickettsial diseases, cat-scratch disease, and *Spirillum minus* (rat bite fever), among others.

Lessons for the Clinician

- Tularemia should be considered in the differential diagnosis of lymphadenopathy, especially in the summer months, when there is increased risk of tick bites.
- Inquire about tick bites and examine closely for hidden lesions on the scalp in all children with acute cervical lymphadenitis.

- Test for tularemia if lymphadenitis is not improving with appropriate antistaphylococcal coverage.
- Tularemia can be transmitted from a cat scratch or bite and should be considered in the differential diagnosis of cat-scratch disease.
- Avoid tick bites and contact with sick and dead animals (rabbits, squirrels, etc)

Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/40/4/197.

ANSWER KEY FOR APRIL 2019 PEDIATRICS IN REVIEW

Cough: 1. D; 2. B; 3. A; 4. D; 5. D.

Tuberculosis in Children: 1. C; 2. C; 3. A; 4. C; 5. D.

Nontuberculous Mycobacterial Infections in Children: 1. D; 2. A; 3. C; 4. D; 5. B.

Case 3: Two Preschoolers with Fever

Shraddha Mittal, Lauren Marlowe, Dustin Elliott, Deana Gifford, Kristen Ritenour
and Howard Topol

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4 Chronic Dysphagia and Weight Loss in a 3-year-old Boy

Sarah Mancone, MD,* Neelima Tummala, MD,* Thomas Pranikoff, MD,†
Drew P. Plonk, MD*

**Department of Otolaryngology and †Department of Pediatric Surgery, Wake Forest Baptist Medical Center, Winston-Salem, NC*

PRESENTATION

A 3-year-old boy presents to the emergency department with a 1-year history of dysphagia. Per his father, the boy has developed "strange eating habits" where he will place both juice and food into his mouth, swallow the liquid component, and spit out the solid components. Other associated symptoms include spitting up of saliva and progressive weight loss. There is no known history of throat pain, breathing problems, choking episodes, or witnessed foreign body ingestion. The boy has been previously seen by multiple pediatric providers, who attributed his spitting up, decreased oral intake, and weight loss to severe reflux, leading to repeated trials of antacid therapy without improvement in symptoms. Physical examination findings are normal except for the patient appearing malnourished and small for his age.

DISCUSSION

Differential Diagnosis

The differential diagnosis of a child presenting with gastrointestinal (GI) complaints such as dysphagia, recurrent emesis or spitting up, and weight loss is broad and includes gastroesophageal reflux disease, mechanical obstruction, migraine headaches, and food allergy, among other etiologies. A cause more commonly encountered in the acute setting but possible in the chronic setting is esophageal foreign body (EFB).

Actual Diagnosis

For this patient, the decision was made to proceed with an upper GI radiologic study, and a scout film revealed the presence of a radiopaque EFB that had the typical, circular shape of a coin but an unusual moth-eaten appearance (Fig 1). With this finding, a diagnosis of a chronic EFB after unwitnessed foreign body ingestion was made.

The Condition

Pediatric EFBs are exceedingly common. The American Association of Poison Control Centers reported more than 116,000 ingestions in 2000, and approximately 1,500 deaths per year in the United States are attributed to foreign body

AUTHOR DISCLOSURE Drs Mancone, Tummala, Pranikoff, and Plonk have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Mancone's current affiliation is Department of Internal Medicine, Yale-New Haven Hospital, New Haven, CT.

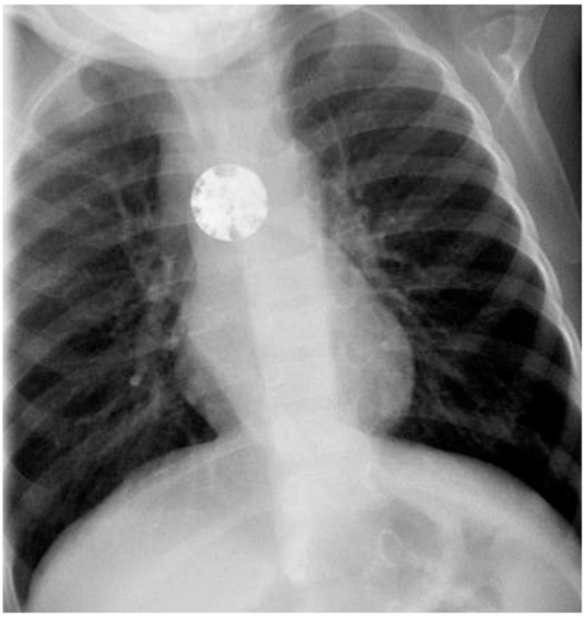

Figure 1. Scout film demonstrating a foreign body in the esophagus.

ingestion. This condition is largely associated with infants and young children, with 75% of these ingestions occurring in children aged 5 years or younger. This peaks during the ages of 6 months to 3 years. (1)(2) The most commonly ingested object by children in the United States is the coin, with 1 study reporting more than 250,000 coin ingestions and 20 deaths across 10 years. (1) This problem is so common, in fact, that it has been estimated that 4% of all children will at some point swallow a coin. (3)

Fortunately, the number of deaths from pediatric EFBs remains low. Most ingestions are witnessed or have clear symptoms of foreign body ingestion, allowing for early intervention. Many EFBs are also cleared spontaneously, including approximately 30% of ingested coins. (1) An estimated 40% of pediatric foreign body ingestions are unwitnessed, however, and up to half of all EFBs may not produce any symptoms. (2)

The symptoms of EFB are widely variable according to the object's shape and size as well as the patient's age. The likelihood of spontaneous clearance of a swallowed coin, for instance, decreases with coins larger than 23.5 mm (eg, a quarter) and in children younger than 5 years. (1) In addition, most EFBs are found at the thoracic inlet, indicating that foreign bodies that travel beyond this point are most likely to pass without incident. In a study by Dedhia, et al, (4) 72.2% of coins were found in the proximal esophagus, and coins in the distal esophagus were 9.3 times more likely to pass spontaneously than coins in the proximal esophagus. Symptoms of acute EFB include, but are not limited to, blood in saliva; coughing; drooling; dysphagia or odynophagia; failure to thrive; fever; food refusal; foreign body sensation in the throat; gagging; irritability; pain in the neck, throat, or chest; recurrent aspiration pneumonia; respiratory distress; stridor; tachypnea or dyspnea; vomiting; and wheezing. (2) In a study by Little et al, (5) the most common presenting symptoms were dysphagia (37%), drooling (31%), and choking (17%). In a study by Sink et al, (6) the most common presenting symptoms were choking/gagging (49%), vomiting (47%), dysphagia and odynophagia (42%), cough (40%), and drooling (40%). Notably, the overlap in symptoms observed between these studies is minimal, and neither of these studies had consistent symptoms seen in more than half of the patients observed.

The presentation is further complicated by differences in symptoms seen with acute versus chronic EFBs. In a retrospective review by Miller et al, (3) 76% of patients with chronic EFBs presented with respiratory symptoms as the primary complaint, including respiratory distress, asthmatic symptoms, and cough. However, 22% of patients with chronic EFBs reported primarily GI symptoms such as nausea, vomiting, and dysphagia, and 1 patient in this study was asymptomatic. Both groups of patients (respiratory and GI complaints), though, had worsening of symptoms with meals. This variability was further seen in a study by Louie et al, (7) in which a history of wheezing and fever had the strongest association with unwitnessed EFB.

Local inflammation caused by chronic EFBs increases the risk of serious complications. Inflammation can progress to erosion and eventually complete perforation through the esophagus. Potential sequelae of esophageal erosion include stricture and diverticulum formation, which can result in dysphagia, food impaction, aspiration, recurrent pneumonia, and failure to thrive. Complete perforation can result in tracheoesophageal fistula formation, with a similar detriment to pulmonary health, and erosion to the adjacent aorta can lead to exsanguination and death. Even if the object passes through the esophagus there can be injury to esophageal mucosa. Sharp objects can lead to bowel obstruction, perforation, and erosion into adjacent organs.

The GI disorders related to a chronic EFB are also consistent with those that can lead to feeding disorders. According to a review by Manikam and Perman, (8) feeding disorders can occur in healthy children, children with GI disorders, and very commonly in children with developmental delays. Most feeding disorders have organic causes, but evidence has shown that many can be attributed to psychosocial factors and family dynamics. Even when the cause is organic, feeding disorders can be greatly improved with treatment of the medical condition as well as behavior therapy to modify the child's learned feeding patterns and parent education.

Studies have shown that the risk of complications can be directly correlated with the duration of time that the object remains in the esophagus. A retrospective analysis by Denney et al (9) found that esophageal ulceration was seen with 15.5% of coins present in the esophagus for less than 12 hours, 22.6% of coins present 12 to 24 hours, and 45.5% of coins present for greater than 24 hours. These data support the need for early diagnosis and intervention by pediatric health-care providers.

Treatment/Management

The treatment for both acute and chronic EFBs is rigid or flexible esophagoscopy with removal of the foreign body under direct visualization. Once the patient has had the foreign body removed and has been stabilized surgically, management is largely supportive.

Patient Course

Otolaryngology was consulted and the child was taken to the operating room. Rigid esophagoscopy was performed, and the foreign body, consistent with a penny, was encountered in the mid esophagus, approximately at the location of the thoracic inlet. A forceps was used to grasp the penny, but the coin immediately fractured. The fracturing of the coin during removal and its moth-eaten appearance on plain film (Fig 1) were consistent with likely acid breakdown of the coin's metal alloy of copper and zinc. The fragment was removed, and the remainder of the coin was grasped and slowly worked free from surrounding granulation tissue involving the esophageal mucosa (Fig 2). After removal, the esophagoscope was advanced again to visualize the area. The presence of substantial erosion and granulation was verified, although complete perforation was not evident. To complete the procedure, a nasogastric tube was placed under direct visualization to allow for postoperative feeding access, bypassing the area of concern. Three days after surgery, a barium esophagram was performed, which revealed a contained perforation, or pseudodiverticulum.

The patient was discharged from the hospital on a liquid diet by mouth with enteral nutrition via a nasogastric tube for supplementation. Serial barium esophagram studies were performed during the next 3 months and showed ongoing severe reflux and unchanged pseudodiverticulum secondary to the chronic EFB. Due to concern by the treatment team that ongoing, uncontrolled reflux would impair healing and potentially lead to perforation, Nissen fundoplication and gastrostomy tube placement were performed. The pseudodiverticulum remained unchanged, and his clinical course remained benign. He was started on feedings by mouth, which he tolerated, and 6 months after his foreign body was identified his gastrostomy was removed. Surgery to repair the diverticulum was no longer recommended given his stable diverticulum without symptoms.

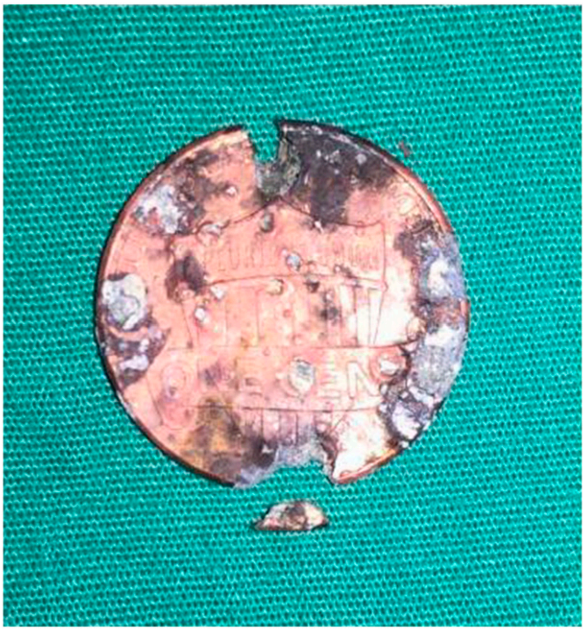

Figure 2. Photograph of a coin and a coin fragment after removal from the esophagus.

Lessons for the Clinician

- Esophageal foreign bodies (EFBs) are common in the pediatric population and when promptly diagnosed and treated typically result in minimal morbidity and mortality.
- Typical EFB scenarios of witnessed ingestion, obvious choking, or complete food aversion do not always occur, as exemplified by this case of a child presenting with intermittent spitting up and chronic weight loss.
- Given the large variability in presentation of this condition and the severe complications associated with chronic EFBs, pediatricians and other pediatric health-care providers should maintain a high index of suspicion for foreign body ingestion when treating a young child with gastrointestinal or respiratory symptoms of unknown etiology and should consider imaging, such as a chest radiograph or even an upper gastrointestinal radiologic study, relatively early if symptoms persist despite treatment.

References for this article are at http://pedsinreview.aappublications.org/content/40/4/202.

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Sarah Mancone, Neelima Tummala, Thomas Pranikoff and Drew P. Plonk

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Water Safety

Emma A. Omoruyi, MD, MPH*
**Department of Pediatrics, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX*

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Drowning is the second leading cause of unintentional injury in children. Children 1 to 4 years old are the most vulnerable age group to die of drowning. Minority children are most vulnerable to these types of injuries and fatalities, and their rate of a fatal unintentional drowning injury is significantly higher than that of their white peers The factors that have caused this racial disparity include minority children's lack of access to swimming pools, lack of availability and promotion of swimming lessons, and lack of participation in water-related recreational activities. This population's vulnerability increases when exposed to unsupervised bodies of water. For every childhood drowning death there are 5 children who will be hospitalized for submersion injuries. Severe submersion injuries can result in brain injuries that have long-term consequences, including learning difficulties and permanent loss of basic functioning.

Lack of protection, preparation, and prevention increases the risk of drowning. Children aged 1 to 4 years are most likely to drown in home swimming pools. Pool owners should protect this area by removing toys, floats, and games around the deck that might be attractive to unsupervised young children. There is strong evidence that proper pool barriers prevent accidental access by young children. Swimming pools should be surrounded by isolated fences (all 4 sides) that are dynamic and secure. The fence should be at least 4 feet high, gates should be self-latching and face outward, and latches should be out of reach to young children. Four-sided fencing has been shown to reduce the risk of drowning by 83% compared with 3-sided property line fencing. Soft inflatable pools provide an increased risk because children can lean over the soft sides of the pool and fall in, and these types of pools are typically not properly protected by gates or fencing. Moreover, these types of inflatable pools often hold large amounts of water for an extended period, extending the period of risk. There is not enough data to determine the effectiveness of supplemental pool alarms and rigid pool covers. A 4-sided fence remains the best protection.

Research has also shown that preparation through formal swimming lessons reduces the risk of drowning. The position of the American Academy of Pediatrics (AAP) had been that formal swimming lessons should start when the child is developmentally ready, typically after the child's 4th birthday. Previously there had been a concern that swimming lessons too early in childhood can create a false sense of security in parents and possibly inhibit a child's fear of the water. However, due to recent evidence that swimming lessons in 1- to 4-year-olds may provide a reduction in drowning risk, the AAP has recently relaxed its suggestion on the age at which children can begin water survival skills training. Ultimately there is not enough research to support a stance that all 1- to 4-year-old children receive swim lessons. Moreover, strong swimming skills in infants and toddlers should never supersede adult supervision and pool barriers.

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Prevention through education is another key to reducing drowning mortalities. Drowning can occur anywhere there is water (bucket, bathtub, pool, lake, water collection on side of road, etc), so even after children successfully complete formal swimming lessons they should continue to be closely supervised when near water. The percentage of natural water drownings increases with age, and teenagers are more likely to drown in a lake, river, or ocean than in a pool. Use of Coast Guard–approved life jackets is imperative during boating activities. Parents should be told that air-filled or foam water toys (noodles, inner tubes, water wings) are not designed to be life jackets and will not keep a swimmer safe during a submersion event. Older swimmers should be taught how to monitor weather conditions, obey natural water warning signs, avoid unsupervised locations, and swim with a buddy. In addition, they should understand that alcohol use can impair judgment.

Pediatricians should provide water safety counseling as part of routine anticipatory guidance at different ages and stages of development. Key messages that the AAP recommends include the following: 1) Never leave small children unsupervised around any water. Water should be emptied from containers after use. Bathroom access should be limited to small children to prevent drowning in toilets and filled bathtubs. 2) Families who own pools should be strongly advised to secure all 4 sides with a well-maintained, climb-resistant fence and a self-latching gate that opens away from pool. Movement of the gate away from the pool increases the difficulty for the child to successfully disengage the latch and pull the gate open. 3) Families who have access to a community pool or who own a portable, above-ground pool should be counseled about the hidden dangers (ie, lack of protective barriers). 4) Encourage parents to enroll their children in swimming lessons when developmentally ready. 5) Children should be taught to never swim alone or without adult supervision. 6) Adults with swimming skills should be at arm's length to infants and toddlers near bodies of water. Adult supervisors should not be distracted by cell phones, socializing, or drinking alcohol. Ideally, adult supervisors should also know cardiopulmonary resuscitation in addition to having strong swimming skills. The ideal ratio of adults to children is 1:1, but the recommended ratio can vary based on age and jurisdiction. 7) The safest location for recreational swimming should have a lifeguard close by. 8) Small children and nonswimmers should wear life jackets when near water and for anyone who accesses a watercraft. 9) Air-filled swimming aids are not a substitute for a US Coast Guard–certified life jacket. 10) Swimmers should know the depth of the water because jumping and diving can cause injury in shallow water. They should also know the weather tides, waves, and water currents when going into a natural body of water. 11) Avoid activity on top of weak or thawing ice. 12) Children with underlying medical problems, such as seizure disorders, should be monitored closely near water, and older children should be encouraged to take showers instead of baths.

Legislative advocacy efforts should focus on mandating 4-sided isolation programs and the requirement that all public pools be monitored by a lifeguard. The United States does not have any federally mandated laws requiring 4-sided pool fencing, and individual states vary in their degrees of legislation.

COMMENT: This comprehensive *In Brief* is an excellent review of water safety and the importance of the anticipatory guidance that pediatricians can provide. The summary reinforces that the drowning risk increases with inability to swim, lack of pool barriers, lack of close supervision, failure to use life jackets, use of alcohol, and having a seizure disorder. Bathtubs are the highest site of drowning for those with seizure disorders, so showering should be the preferred method if the child is not supervised. Pediatricians have access to a variety of resources through the Injury Prevention Program (TIPP sheets) of the AAP, the Centers for Disease Control and Prevention (CDC), the Consumer Product Safety Commission, and the US Coast Guard. Although this guidance is important to all parents, as drowning risk is present in any accumulation of water, such as buckets, toilets, and bathtubs, drowning is the leading cause of death in 1- to 2-year-olds in Arizona, California, Florida, and Texas, where warm weather and access to pools and bodies of water may occur year-round. Points to be reinforced include the importance of emptying water out of buckets and bathtubs; that children should never be left alone in the bathtub or sink, even for a few seconds; and that adults should always remain at arm's length if a young child is in water of any kind. Finally, parents are role models for their children, so their actions while swimming and use of US Coast Guard–approved flotation devices while boating serve as examples that their children will strive to emulate.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

Water Safety

Emma A. Omoruyi

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Hyperinsulinism

Dominique Long, MD, Yasmin Akhtar, DO
Johns Hopkins Hospital, Baltimore, MD

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Hyperinsulinism (HI), the most common cause of hypoglycemia in children, is an excess of insulin secretion from the pancreatic β cells, and it can be congenital or acquired. Congenital HI, which can be transient or persistent, is associated with a risk of permanent brain injury as high as 25% to 50% if there is a delay in diagnosis or inadequate treatment, making early recognition essential. Brain damage occurs because insulin functions to decrease glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis, all of which deprive the brain of its primary and secondary energy sources (glucose and ketone bodies). A plasma glucose (PG) level less than 50 mg/dL (<2.8 mmol/L), a detectable serum insulin level, a low plasma β-hydroxybutyrate level less than 2.0 mmol/L, and low free fatty acid levels less than 42 mg/dL (<1.5 mmol/L) are diagnostic of HI.

The incidence of congenital HI varies between 1 in 50,000 births in Holland and 1 in 2,500 in Saudi Arabia. Sixty percent of patients are diagnosed in the first week of life, 30% in the first year of life, and 10% in adulthood. Because HI often presents in the neonate, it is important to differentiate it from transitional hypoglycemia of infancy, which is a physiologic transition of glucose regulation as infants adapt to extrauterine life. Normally, neonates initially maintain PG levels at 55 to 65 mg/dL (3.1–3.6 mmol/L), which increases to greater than 70 mg/dL (3.9 mmol/L) by 2 to 3 days after birth with little variation in relation to time from last feed. When it occurs, transitional hypoglycemia of infancy lasts 12 to 24 hours, is not associated with brain damage, and usually appears in appropriate-for-gestational age babies who are nondistressed.

Transient HI occurs in certain high-risk infants: premature infants, infants of diabetic mothers or mothers with a history of toxemia, small- or large-for-gestational age infants, and infants who have experienced difficult birth/birth asphyxia. Sulfonylureas or intravenous glucose infusions administered to mothers during labor can also cause transient HI. Symptoms in infants, often subtle, include jitteriness, tachycardia, pallor, hypothermia, lethargy, irritability, poor feeding, cyanosis, tachypnea, apnea, weak/high-pitched cry, floppiness, eye rolling, lip smacking, and seizures. Older children experience tremulousness, anxiety, tachycardia, palpitations, sweating, paresthesia, hunger, and behavioral changes.

In addition to HI, the differential diagnosis for hypoglycemia includes hormonal deficiencies (growth hormone and cortisol), inborn errors of metabolism, fatty acid oxidation defects, exogenous insulin administration, insulinomas, dumping syndrome–associated hypoglycemia, and drug ingestions. Associated clinical features and family history can often help guide the diagnosis: for example, midline facial defects and micropenis suggest hypopituitarism, and hepatomegaly raises concern for a glycogen storage disease. The presence of certain syndromes and hypoglycemia occurring less than 4 to 6 hours from the last feed suggest HI.

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Congenital Hyperinsulinism: Current Status and Future Perspectives. Yorifuji T. *Ann Pediatr Endocrinol Metab.* 2014;19(2):57–68

The most common syndrome associated with HI is Beckwith-Wiedemann syndrome (BWS) (Table), a fetal overgrowth syndrome caused by an imprinting defect in the chromosome 11p15.5 region. HI in BWS, which occurs in approximately 50% of patients, is usually transient but can be persistent and severe, and it is thought to be secondary to loss of function of KATP channels, leading to dysregulated insulin secretion. HI is also associated with Kabuki syndrome, Turner syndrome, and multiple endocrine neoplasia syndromes, as well as Sotos, Costellos, Simpson-Golabi-Behmel, and Usher syndromes, and also trisomy 13 and congenital disorders of glycosylation.

Because plasma insulin levels are often not definitively elevated, the diagnosis of HI depends on obtaining blood at

TABLE. **Genetic Mutations Associated with Hyperinsulinism**

CHANNEL	MUTATION	INHERITANCE	DIAZOXIDE RESPONSIVE	MODY	CLINICAL FEATURES	SYNDROME
KATP/SUR1	ABCC8	AR/AD/sporadic	– or +/– or –		Paternal transmission: resection	
KATP/Kir6.2	KCNJ11	AR/AD/sporadic	– or +/– or –			
GDH	GLUD1	AD	+		Hyperammonemia/leucine sensitive	
GCK	GCK	AD	–	Activating mutation HI/inactivating mutation MODY 2		
SCHAD	HADH1	AR	+			
UCP2	UCP2	AD	+			
HNF4A	HNF4A	AD	+	Type 1	LGA	
HNF1A	HNF1A	AD	+	Type 3		
MCT1	SLC16A1	AD	–		Hypoglycemia triggered by exercise	
HK1	HK1	AD	+			
PGM1	PGM1	AR	–			
KATP	IGF2/H19/CDKN1C/KCNQ1	Sporadic	+/–		Omphalocele, macroglossia, macrosomia, renal abnormalities, and visceromegaly	BWS
Kabuki	KMT2D/KDM6A	Sporadic	+/–		Long palpebral fissure, arched eyebrows, eversion of the external one-third of the lower lid, skeletal abnormalities, neurodevelopmental delay and intellectual disabilities, abnormal GH and thyroid levels, and premature thelarche	
CDG1a	PMM2	AR	+			
CDG1b	MPI	AR				

AD=autosomal dominant, AR=autosomal recessive, BWS=Beckwith-Wiedemann syndrome, CDG=congenital disorders of glycosylation, GCK=glucokinase, GDH=glutamate dehydrogenase, GH=growth hormone, HI=hyperinsulinism, HK=hexokinase, HNF=hepatocyte nuclear factor, KATP=potassium adenosine triphosphate, LGA=large for gestational age, MCT=monocarboyxlate transporter, MODY=maturity onset diabetes of the youth, PGM1=phosphoglucomutase, SCHAD=short chain 3-hydroxyacyl CoA dehydrogenase deficiency, SUR=sulfonylurea, UCP2=uncoupling protein.

the time of hypoglycemia for pertinent laboratory testing. When the PG level is less than 50 mg/dL (2.8 mmol/L), serum insulin, C-peptide, bicarbonate, lactate, free fatty acid, and β-hydroxybutarate levels should be measured. Cortisol and growth hormone levels are also useful to rule out central hormone deficiency: both should be elevated at the time of hypoglycemia. After the critical sample is drawn, a glucagon stimulation test should be performed by administering 1 mg of glucagon, either intramuscularly or intravenously, and monitoring PG levels every 5 minutes for 30 minutes. A PG level increase of at least 30 mg/dL (1.7 mmol/L) after glucagon administration is consistent with HI.

The normal release of insulin in response to PG is a complex process. Initially, glucokinase in the β cells of the pancreas senses the glucose level. High glucose levels lead to increased expression of glucose transporters (GLUT2) on the β cell, which take up glucose. Glucose is then metabolized, causing an increase in the ratio of adenosine triphosphate (ATP) to adenosine diphosphate (ADP), leading to closure of the ATP-dependent potassium (KATP) channels in the β-cell membrane. The rise in the ATP to ADP ratio causes membrane depolarization and influx of cellular calcium, and leads to fusion and secretion of insulin outside the cell. In addition to the KATP channel, there are other proteins in the β cell that help with normal insulin secretion. A mutation affecting any of these steps can dysregulate insulin secretion, so looking for a genetic etiology in the presence of hyperinsulinemic hypoglycemia has become the standard of care (Table).

Some genes associated with congenital HI can also lead to monogenic diabetes (maturity-onset diabetes of the young). Examples include inactivating mutations in glucokinase or in hepatocyte nuclear factors 1A and 4A, which lead to congenital HI, which then transitions to monogenic diabetes in adulthood. Also, a mutation that activates KATP channel subunits can cause either severe neonatal diabetes or a mildly increased susceptibility to adult-onset diabetes.

Goals of treatment in congenital HI include maintaining a PG level greater than 70 mg/dL (3.9 mmol/L) and establishing a normal feeding regimen with a tolerance for fasting appropriate for age. Acutely, blood glucose levels must be stabilized to prevent brain damage and to allow time for further diagnosis so that specific therapy can be initiated, which may include dietary, medical, or surgical approaches. Parenteral glucose may be necessary, often at rates as high as 15 to 25 mg/kg per minute. If the child with HI also has a feeding disturbance, food aversion, or gastroesophageal reflux disease, food may need to be given via nasogastric tube to maintain euglycemia. With emergent hypoglycemia, glucagon can be administered at a dose of 0.5 to 1.0 mg subcutaneously or intramuscularly.

When possible, the long-term management of HI benefits from the expertise at a tertiary care center (Fig). Treatment depends on whether the patient is diazoxide responsive. Management in diazoxide-unresponsive patients may depend on genetic testing for a mutation underlying the congenital HI. Diazoxide is the first-line treatment for controlling hypoglycemia. It works by causing KATP channels to open, thereby reducing insulin secretion; however, it is ineffective with diffuse disease from inactivating mutations in ABCC8 and KCNJ11 (Table). Diazoxide is started at a dose of 5 to 15 mg/kg per day divided twice per day, to a maximum dose of 20 mg/kg per day. Before a patient is labeled as unresponsive, diazoxide should be given at the maximum dose for 5 days. Adverse effects of diazoxide use include hypertrichosis (reversible once off therapy) and fluid retention, which can be especially problematic in infants, leading to congestive heart failure and pulmonary hypertension. Chlorothiazide (5–10 mg/kg per day in 2 divided doses) is often started at the same time as diazoxide to mitigate fluid retention and has the advantage of also suppressing insulin secretion.

For diazoxide-unresponsive HI, octreotide is a long-acting somatostatin analog that binds the SSTR5 receptor and reduces insulin synthesis in pancreatic β cells. The recommended dose is 5 to 35 μg/kg per day given subcutaneously in divided doses or by continuous infusion. Tachyphylaxis occurs but is transient. Octreotide therapy can have serious adverse effects, including abdominal pain, nausea, diarrhea, hepatitis, long QT, and necrotizing enterocolitis. With severe HI, glucagon can be used in combination with octreotide, both acutely and as a long-term infusion. A recent report describes 2 patients unresponsive to diazoxide and octreotide who were successfully treated with sirolimus, also known as rapamycin. Exendin, a glucagon-like peptide receptor antagonist, may have a role to play in managing hypoglycemia from HI.

Indications for surgery in congenital HI include focal disease confirmed by Fluoro-18-L-Dihydroxyphenylalanine positron emission tomography/computed tomography (18F-DOPA PET/CT) and medically unresponsive diffuse disease. Focal disease is treated with partial pancreatectomy, often performed laparoscopically if the lesion is located in the body or tail of the pancreas.

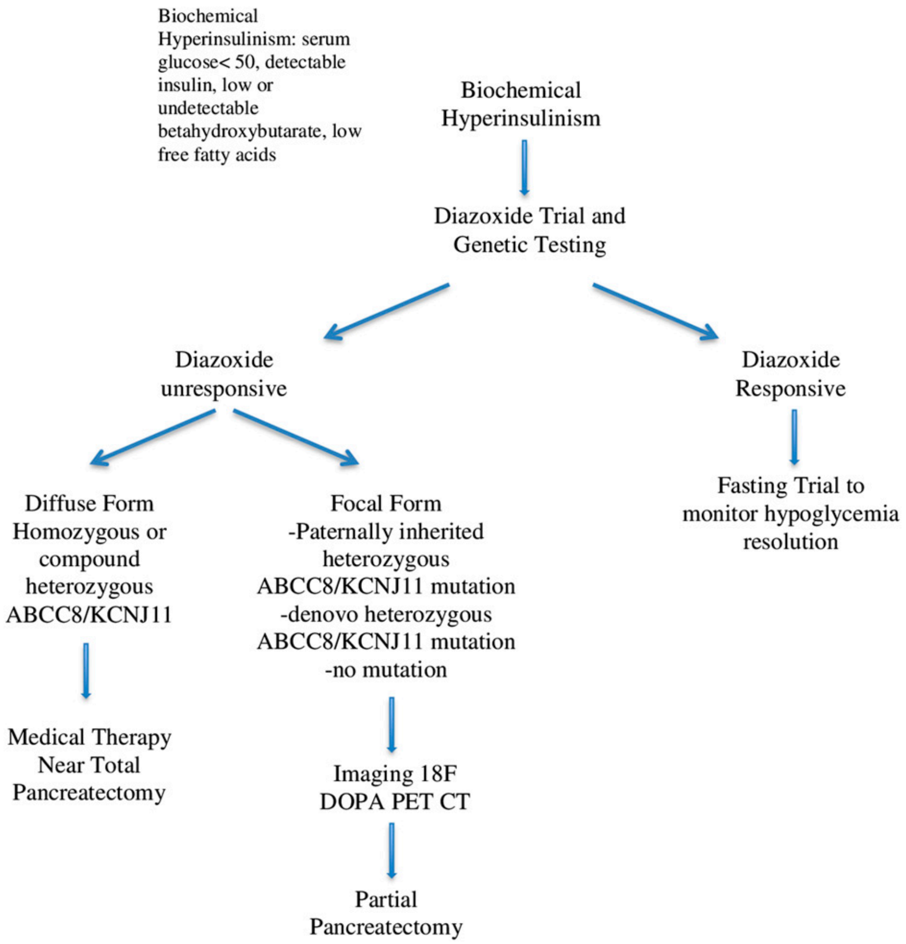
Biochemical Hyperinsulinism: serum glucose< 50, detectable insulin, low or undetectable betahydroxybutarate, low free fatty acids
Biochemical Hyperinsulinism
Diazoxide Trial and Genetic Testing
Diazoxide unresponsive
Diazoxide Responsive
Diffuse Form Homozygous or compound heterozygous ABCC8/KCNJ11
Focal Form -Paternally inherited heterozygous ABCC8/KCNJ11 mutation -denovo heterozygous ABCC8/KCNJ11 mutation -no mutation
Fasting Trial to monitor hypoglycemia resolution
Medical Therapy Near Total Pancreatectomy
Imaging 18F DOPA PET CT
Partial Pancreatectomy

Figure. Algorithm for treatment of hyperinsulinism.

Near-total pancreatectomy is the last resort for medically unresponsive diffuse HI. Patients often continue to experience hypoglycemia even after 95% to 98% pancreatectomy, but the hypoglycemia is likely to be less frequent or severe. Surgery entails a high risk of exocrine pancreatic insufficiency and diabetes mellitus.

COMMENT: With an incidence estimated to be 1 of 13,700 births, BWS is relatively rare, but, as Drs Long and Akhtar report, it is the most common syndrome associated with HI. This interesting syndrome also has multiple other associations, as evidenced by the number of times it is mentioned even in other *In Briefs* that I have personally edited (Abdominal Masses, Apnea, Cushing Syndrome, Growth, Neonatal Hypoglycemia, Tuberculosis, Tumor Markers, Wilms Tumor), as well as in more than a few articles and *Index of Suspicion* pieces. For a rarity, it pops up in *Pediatrics in Review* more often than we would likely expect.

A syndrome of overgrowth resulting from either genomic or epigenetic changes to chromosome 11p15, BWS usually comes without a positive family history: most cases reflect loss of methylation on the mother's chromosome, or uniparental disomy from the father. In addition to hypoglycemia, the syndrome may be marked by macrosomia, hemihypertrophy, macroglossia, visceromegaly, enlargement of the adrenal cortex, kidney abnormalities, and a propensity for embryonal tumor growth, particularly Wilms tumor and hepatoblastoma. Affected children may also have umbilical hernias and abnormal pits or creases of the ear lobe.

– Henry M. Adam, MD
Associate Editor, *In Brief*

Hyperinsulinism

Dominique Long and Yasmin Akhtar

Pediatrics in Review 2019;40;207

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Hyperinsulinism

Dominique Long and Yasmin Akhtar

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Infant Peanut Introduction Simplified

Wade T.A. Watson, MD, MEd,* Edmond S. Chan, MD†

*Division of Allergy, Department of Pediatrics, Dalhousie University, IWK Health Centre, Halifax, Nova Scotia, Canada

†Division of Allergy and Immunology, Department of Pediatrics, University of British Columbia, BC Children's Hospital, Vancouver, British Columbia, Canada

Practice Gaps

1. To reduce the risk of developing peanut allergy in infants, clinicians should be able to advise families of the current recommendations for when, where, and how to introduce peanut into the infant's diet.
2. Clinicians should recognize infants at high risk for developing peanut allergy and should be able to either appropriately investigate and manage peanut introduction or facilitate a referral to an allergy specialist for further investigations/advice.

Objectives

After completing this article, readers should be able to:

1. Define an infant at risk for developing peanut allergy.
2. Describe recent evidence to support early peanut introduction to infants.
3. Using the updated National Institute of Allergy and Infectious Diseases–sponsored guidelines, advise parents when, where, and how to introduce peanut into their infant's diet.
4. Identify and refer infants at high risk for developing peanut allergy to an allergy specialist for further education/advice.
5. Discuss challenges to implementation of these guidelines in clinical practice.
6. Use practical tips to make peanut introduction into an infant's diet easier to accomplish.

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ABBREVIATIONS

IgE	immunoglobulin E
LEAP	Learning Early About Peanut Allergy

INTRODUCTION

Approximately 2% of children in the United States are diagnosed as having a peanut allergy. (1) Anaphylaxis is a known complication of peanut ingestion in afflicted individuals. Although overall mortality due to peanut allergy is low, (2) the fear of a life-threatening anaphylactic reaction is high, contributing to the psychological burden of this condition and affecting quality of life and daily activities for children and their families. (3)(4)(5)(6)(7)

In an attempt to reduce the incidence of peanut allergy, early American Academy of Pediatrics clinical practice guidelines recommended delaying the

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introduction of peanut-containing foods until age 3 years. (8) These guidelines were based on expert opinion only, with little evidence to support them. While these guidelines were in force, the incidence of peanut allergy did not change or may have, ironically, increased. After publication of the Learning Early About Peanut Allergy (LEAP) study, (9) the National Institute of Allergy and Infectious Diseases sponsored addendum guidelines for the introduction of peanut in infants. (10) We reviewed and simplified these guidelines in the hopes that a more practical approach will make instructions for peanut introduction easier for families, primary care providers, and pediatricians.

Note that there are also updated general recommendations for early introduction of foods to prevent food allergy. The focus of this review article is peanut introduction. For further information we refer the reader to a more general article on this topic. (11)

DEFINING AN INFANT AT RISK FOR DEVELOPING PEANUT ALLERGY

Infants are considered to be at high risk if they have been diagnosed as having severe eczema or egg allergy. (10) Severe eczema is defined as "persistent or frequently recurring eczema with typical morphology or distribution assessed as severe by a health care provider and requiring frequent need for prescription-strength topical corticosteroids, calcineurin inhibitors, or other anti-inflammatory agents despite appropriate use of emollients." (10) Infants are at risk of peanut allergy if they have mild or moderate eczema. (10) Of note, family history of allergy is a risk factor for the development of allergic conditions but is not specific for peanut allergy. A family history of allergy or peanut allergy should not be used to define risk of peanut allergy in infants.

Eczema in infants is identified as a significant risk factor for the development of food allergies. (12) Early cutaneous exposure to food allergens may result in allergic sensitization, whereas early oral consumption of the same food may result in tolerance. (13) The dual-allergen exposure hypothesis (13) proposes that the timing and balance of these routes of exposure to a food will determine the development of food allergy or tolerance.

EVIDENCE SUPPORTING THE EARLY INTRODUCTION OF PEANUT

Using a questionnaire-based survey, the prevalence of peanut allergy was found to be significantly higher in Jewish children in the United Kingdom compared with Jewish children in Israel by a factor of almost 10. (14) The authors of this study proposed that this difference in prevalence was related to earlier and more frequent peanut exposure in the first year of life in infants in Israel compared with infants in the United Kingdom.

The LEAP study reported the results of a UK study of 640 high-risk infants who were either randomized to early (age 4–11 months) or delayed (avoidance until age 5 years) introduction of peanut into their diet. Consuming peanut early and regularly, as in 3 times weekly, reduced the development of peanut allergy by 86% by 5 years of age compared with the group of children who delayed peanut consumption. (9) The LEAP-On study investigated whether children who had consumed peanut in the primary trial would remain protected from peanut allergy after they stopped eating peanut for 12 months. (15) The benefits of early peanut introduction persisted for the 12 months of this study.

PEANUT INTRODUCTION: THE FINER DETAILS

Low-Risk Infants (No Eczema or Food Allergy)

Most infants (approximately 87%) are at low risk. (16) Age-appropriate peanut-containing food can be introduced at home with other solid foods as the family would do normally. Six months of age is a reasonable age if the infant is tolerating other solid foods. See the Table for suggestions on how to prepare peanut-containing foods that are appropriate for this age group. If tolerated, peanut-containing food should be eaten regularly, at least 3 times per week.

At-Risk Infants (Mild-to-Moderate Eczema)

Approximately 12% of all infants are at risk. (16) Age-appropriate peanut-containing food introduction should occur at home around 6 months of age after determining the infant's ability to tolerate other solid foods. (10) No special evaluation is required. Some care providers may want a physician assessment owing to other factors, such as parental anxiety. The goal of this physician assessment is to reassure the caregiver about the change in the advice about peanut introduction and the safety of giving peanut-containing food at this age at home. If the care provider's anxiety remains high, a supervised feeding in the office may be appropriate. See the Table for appropriate peanut-containing foods. If tolerated, peanut-containing food should be eaten regularly, at least 3 times per week.

High-Risk Infants (Severe Eczema or Egg Allergy)

Few infants (approximately 0.9% of all infants) are high risk. (16) Special considerations need to be given to this group only. Age-appropriate peanut-containing food should be introduced as early as age 4 to 6 months in

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TABLE. **Typical Peanut-Containing Foods, Their Peanut Protein Content, and Feeding Tips for Infants**

	BAMBA[A]	PEANUT BUTTER	PEANUTS	PEANUT FLOUR OR PEANUT BUTTER POWDER
Amount containing approximately 2 g of peanut protein	17 g *or* 2/3 of a 28-g (1-oz) bag *or* 21 sticks	9–10 g *or* 2 teaspoons[b]	8 g *or* ~10 whole peanuts (2½ teaspoons of ground peanuts)	4 g *or* 2 teaspoons
Feeding tips	• For a smooth texture, mix with warm water (then let cool) or human milk or infant formula and mash well	• For a smooth texture, mix with warm water (then let cool) or human milk or infant formula	• Use the blender to create a powder or paste	• Mix with yogurt or applesauce
	• Pureed or mashed fruit or vegetables can be added	• For older children, mix with pureed or mashed fruit or vegetables or any suitable family foods, such as yogurt or mashed potatoes	• 2–2½ teaspoons of ground peanuts can be added to a portion of yogurt or pureed fruit or a savory meal	
	• Older children can be offered sticks of Bamba			

[a] *Bamba (Osem, Shoham, Israel) is named because it was the product used in the Learning Early About Peanut Allergy trial and, therefore, has known peanut protein content and proven efficacy and safety. Other peanut puff products with similar peanut protein content can be substituted for Bamba.*

[b] *Teaspoons and tablespoons are US measures (5 and 15 mL for a level teaspoon and tablespoon, respectively)*

Adapted with permission from Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. Ann Allergy Asthma Immunol. *2017;118(2):166–173.e7.*

these infants after they demonstrate readiness for solids (Table). (10)

Before peanut introduction, allergy testing to peanut is strongly recommended (Fig). (10) The preferred method is by skin prick testing by a qualified allergist. In vitro measurement of peanut-specific immunoglobulin E (IgE) levels is a reasonable alternative, especially if access to an allergist is limited, so as not to delay peanut introduction. Obtaining specific IgE levels to foods other than peanut is not recommended because random testing has a poor positive predictive value for diagnosis of food allergy. (17) Such testing could lead to misinterpretation, overdiagnosis of food allergy, and unnecessary dietary restrictions of other foods. (10) This is true for all age groups, especially if performed without a specific history of a potential allergic reaction to the food.

If the peanut-specific IgE level is negative, peanut may be introduced at home or by a supervised challenge in the clinical setting depending on the level of caregiver concern. (10) If tolerated, peanut-containing food should be eaten regularly, at least 3 times per week.

If the peanut-specific IgE level is positive, the infant should be referred to an allergy specialist.

The next step in investigation of these infants should be skin prick testing to peanut. Depending on the results of a skin test, home introduction, supervised feeding or a graded food challenge in the allergist's office, or strict avoidance are appropriate options (Fig). (10)

OUTCOMES

Tolerance

All children who tolerate peanut should continue eating peanut-containing foods regularly to maintain tolerance. The recommendation is 6 to 7 g of peanut protein per week, divided into 3 or more feedings (see the Table for serving suggestions). (10)

Peanut Allergy Confirmed

In infants who have been identified as allergic to peanut after skin testing or oral challenge, strict peanut avoidance and evaluation and management by a specialist are advised (Fig). (10)

SIMPLE GUIDELINES, BUT PERHAPS NOT SO SIMPLE TO IMPLEMENT

Since the publication of these new guidelines, several concerns have been raised about their implementation. Care must be taken to not medicalize the feeding of an infant's

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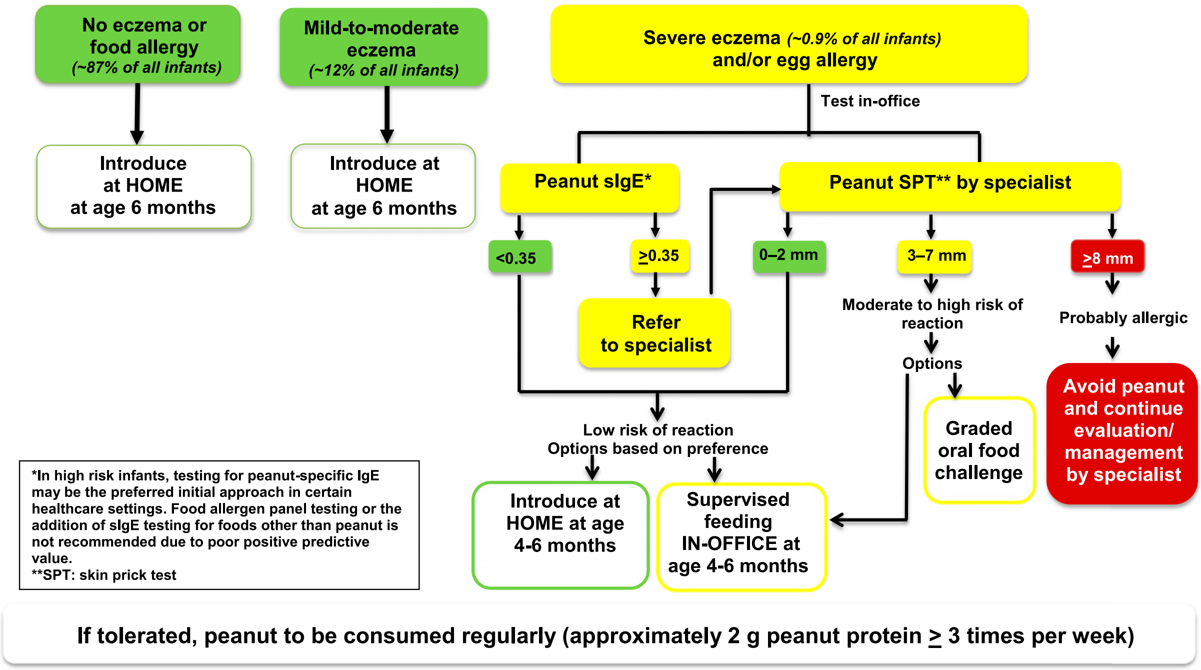
No eczema or food allergy (~87% of all infants)
Introduce at HOME at age 6 months
Mild-to-moderate eczema (~12% of all infants)
Introduce at HOME at age 6 months
Severe eczema (~0.9% of all infants) and/or egg allergy
Test in-office
Peanut sIgE*
Peanut SPT** by specialist
<0.35
≥0.35
Refer to specialist
0–2 mm
3–7 mm
≥8 mm
Moderate to high risk of reaction
Options
Probably allergic
Graded oral food challenge
Avoid peanut and continue evaluation/ management by specialist
Low risk of reaction
Options based on preference
Introduce at HOME at age 4-6 months
Supervised feeding IN-OFFICE at age 4-6 months
*In high risk infants, testing for peanut-specific IgE may be the preferred initial approach in certain healthcare settings. Food allergen panel testing or the addition of sIgE testing for foods other than peanut is not recommended due to poor positive predictive value.
**SPT: skin prick test
If tolerated, peanut to be consumed regularly (approximately 2 g peanut protein ≥ 3 times per week)

Figure. Recommended approaches for when and where to introduce peanut and for the evaluation of children with severe eczema or egg allergy before peanut introduction. (Adapted with permission from Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *Ann Allergy Asthma Immunol.* 2017;118(2):166–173.e7.)

first foods. (18) Other experts have expressed concerns over the definition of the at-risk population, the feasibility and implementation of the guidelines, and the potential for unintended consequences from their implementation. (19)(20)

Severity of Eczema May Be Overestimated

The definition of severe eczema may vary depending on the clinician's or caregiver's experience. Some infants may be misclassified to the high-risk group, leading to unnecessary screening and specialist referrals. (20)(21) Peanut introduction may be delayed, which may result in a missed opportunity for peanut allergy prevention.

How Relevant Is Egg Allergy in Predicting Risk of Peanut Allergy?

Because egg is not a common food consumed at 4 to 6 months of age, the number of infants diagnosed as having an egg allergy is very low. There is no evidence to date that egg allergy is more of a risk factor for developing peanut allergy in infants than is an allergy to, for example, cow milk, a much more common food allergy in this age group. (22)

Overuse and Misinterpretation of Serum Specific IgE Testing

In clinical practice, use of serum specific IgE testing can result in the over diagnosis of food allergy. (19)(23) There is a real risk that a positive peanut-specific IgE level could result in infants being misdiagnosed as having peanut allergy. This, in turn, could result in unnecessary delays in the introduction of peanut and possibly other foods.

Inappropriate Screening/Risk of Screening for Multiple Food Allergies

Infants who are not in a high-risk category may undergo screening, specialist referrals, and oral food challenges due to parental anxiety or clinician overcaution. (23) This could have an effect on the number of specialist referrals and costs to the health-care system. Delays in peanut introduction may also occur.

Caregiver pressure and clinician overcaution may also result in some infants being allergy tested for multiple foods. Because of the risk of false-positive results, foods may be inappropriately not given or removed from the child's diet, leading to loss of tolerance and the development of food allergy. (24)

Early Introduction of Solid Foods Contradicts World Health Organization Recommendations (25)

Current World Health Organization guidelines, (26) as well as many other general pediatric guidelines, (27) recommend exclusive breastfeeding until 6 months of age. The potential

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impact of introducing solid food earlier than the recommended age on the benefits of exclusive breastfeeding, as well as on the total duration of breastfeeding, is not known. The potential benefit of early solid food introduction versus potential risk will need to be individualized according to the infant's risk of developing food allergy. There are no studies to date comparing the introduction of peanut at 4 versus 6 months to see whether one age is better than the other as a means of peanut allergy prevention. (28)

Some Clinicians Will Not Be Comfortable with Infant Oral Food Challenges

Some clinicians will not be comfortable with supervised oral food challenges, especially in infants. (29) For at-risk infants, this rate-limiting step may delay an oral food challenge beyond the 4- to 11-month window and may not provide any benefit of peanut introduction.

Some Caregivers May Not Be Comfortable with the Changed Guidelines

Caregivers may not be aware that the current guidelines recommending early peanut exposure are based on much stronger evidence than the older guidelines that recommended dietary peanut introduction be delayed. Caregivers may remain hesitant and may delay introducing peanut, as well as other solid foods, into their infant's diet. (30)

The Minimum Amount of Peanut Ingestion to Prevent Allergy Has Not Been Established

The 6 g per week recommendation is based on the LEAP study methods. The rationale for choosing this amount is not clear from the study protocol. It is not known whether a smaller amount less frequently would be as effective.

PRACTICAL TIPS TO HELP WITH GUIDELINE IMPLEMENTATION

Most infants can introduce age-appropriate peanut into their diet with no adverse effects. Because this is a major change in advice during the past 18 years, care providers may need to prepare families for this change. Some helpful suggestions include the following:

- As part of anticipatory guidance during health supervision visits, have a discussion about the change in guidelines about peanut introduction.
- Parents may want to do some independent research on the change in peanut feeding recommendations, so provide them with some helpful websites. See the following for some reasonable caregiver-friendly websites:
  http://foodallergycanada.ca/2017/01/important-changes-introduction-peanuts-babies/
  https://community.kidswithfoodallergies.org/blog/new-guidelines-for-early-introduction-of-peanut
  https://preventpeanutallergies.org/
  http://www.nationalpeanutboard.org/news/5-easy-ideas-to-introduce-peanut-to-infants.htm (although the Peanut Board may not be the first site of choice, there are very reasonable suggestions and easy-to-read instructions about how to give peanut to infants)
- Be cautious about overinterpreting the severity of the infant's eczema. Many parents will think their infant's eczema is more severe than it actually is. Of the 13% of infants with eczema, 93% will be mild/moderate and 7% will be severe. Given that most children's eczema is mild to moderate in severity, no special precautions need to be taken.
- Do not get pressured into checking for food allergy other than peanut with high-risk infants. Whereas the risk of false-negative results is very low, false-positive results can occur. Avoidance of irrelevant foods does not help the family.
- If you plan on performing supervised infant peanut challenges in your clinic, practice mixing the peanut-containing food that will be fed to the infant in advance. Previous knowledge of how to mix the foods will make an actual challenge much easier.
- In the at-risk infant group, reactions will be very rare. As with any procedure that may trigger an allergic reaction, have appropriate treatment available (ie, epinephrine 0.01 mg/kg per dose intramuscularly).

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Summary

- To prevent peanut allergy, based on strong research evidence and guidelines, caregivers should introduce age-appropriate peanut at approximately 6 months of age. Most infants can have peanut introduced safely at home and then regular ingestion of peanut several times per week. Delays in accessing specialty care and/or in-office allergy testing should not interfere in this window of opportunity for food allergy prevention.
- Only high-risk infants with severe eczema or egg allergy need in-office testing, medically supervised peanut ingestion, or an oral food challenge. Assistance from an allergist may be needed.
- If an oral food challenge is required, it should ideally be performed as soon as possible.
- Once peanut is introduced and tolerated, peanut should be eaten regularly (eg, 3 times per week) in age-appropriate servings.

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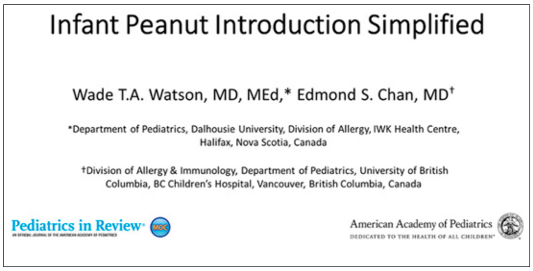

Infant Peanut Introduction Simplified

Wade T.A. Watson, MD, MEd,* Edmond S. Chan, MD†

*Department of Pediatrics, Dalhousie University, Division of Allergy, IWK Health Centre, Halifax, Nova Scotia, Canada

†Division of Allergy & Immunology, Department of Pediatrics, University of British Columbia, BC Children's Hospital, Vancouver, British Columbia, Canada

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1. A 6-month-old boy is brought to the clinic for a health supervision visit. He is born at term with no perinatal complications. Since he was 1 month of age he was noted to have a diffuse, dry, itchy, and scaly rash over the face and extremities, at which time he was diagnosed as having eczema and was prescribed emollients. Since then he has received several courses of topical corticosteroids due to flare-ups and was diagnosed as having severe eczema. At 2 months of age he was seen in the emergency department with acute upper respiratory tract infection, respiratory distress, and wheezing, for which he was admitted to the hospital for 3 days, received supplemental oxygen, and was discharged on a home nebulizer. Family history is positive for asthma and allergic rhinitis in the father. The mother has a history of mild eczema, and the maternal aunt has peanut allergy. Which one of the following factors places this infant at high risk for developing peanut allergy?
   A. History of asthma in the father.
   B. History of mild eczema in the mother.
   C. History of peanut allergy in maternal aunt.
   D. History of severe eczema in the patient.
   E. History of wheezing in the patient.
2. After completing the history and physical examination, the clinician in the vignette in question 1 provides the family with anticipatory guidance, including continued care for the severe eczema. The clinician also discusses introduction of solid foods. The family inquires about the new recommendations for early introduction of peanut. They are worried about introducing new foods, particularly peanut-containing foods because of the history of allergies. Which one of the following is the next best recommendation for peanut-containing solid food introduction to provide in this patient?
   A. Introduce age-appropriate peanut-containing food at home with other foods now; if tolerated, continue to provide peanut-containing food 3 times a week.
   B. Defer the introduction of peanut-containing food until 5 years of age due to severe eczema.
   C. Obtain a random total serum immunoglobulin E (IgE) level before introducing peanut-containing foods.
   D. Refer the infant to an allergist for allergy testing to peanut by skin prick test before the introduction of peanut-containing food.
   E. Supervised feeding of peanut-containing food in the provider's office 3 times a week for 1 month to alleviate parental anxiety.
3. A 4-month-old girl with severe eczema is seen in the office for a routine health supervision visit. The family lives in a rural area, and the nearest pediatric allergist is at the University hospital 4 hours away from their home. The pediatrician orders peanut-specific IgE testing to be performed before the 6-month health supervision visit, which turns out to be negative. In providing recommendations for the introduction of peanut-containing foods, which one of the following is the most appropriate next step in the management of this patient?
   A. Defer the introduction of peanut-containing solid foods until the infant can be seen by an allergist for peanut skin testing.
   B. If the introduction of appropriate peanut food is tolerated, peanut-containing food should not be given more frequently than once a month.
   C. Introduce age-appropriate peanut-containing foods at home starting at 6 months of age.
   D. Introduce age-appropriate peanut-containing food in a supervised setting in the office at 6 months of age after premedicating with diphenhydramine.
   E. Repeat the peanut-specific IgE level 2 months after introducing a peanut-containing food challenge.

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4. A 6-month-old girl with a history of severe eczema comes to the clinic for follow-up of a positive peanut-specific serum IgE level. Which one of the following is the most appropriate next step to be taken by her pediatrician?
    A. Recommend avoidance of peanut-containing food products for life.
    B. Recommend avoidance of peanut-containing food products until the child is 5 years of age.
    C. Delay the introduction of solid foods and order serum IgE levels to other foods.
    D. Refer the patient to a pediatric allergist for skin testing for peanut.
    E. Repeat the peanut-specific serum IgE levels in 1 month.
5. A 4-month-old boy, exclusively breastfed, is seen in the clinic for a routine health supervision visit. He has been healthy, and there is no history of eczema. The mother asks whether she should start to introduce peanut-containing foods into his diet at this age or wait until he is 6 months old. She is concerned about him developing peanut allergy as the paternal grandmother is allergic to peanut. Which of the following is the most appropriate advice to be given to this mother at this time?
    A. Perform a serum peanut IgE level first if the infant is to be started on peanut-containing foods at age 4 months.
    B. Peanut may not be introduced before 6 months of age due to a positive family history of peanut allergy.
    C. The infant should be referred to an allergist for skin testing first if peanut-containing foods are to be introduced at 4 months of age.
    D. There are no studies performed to date that compare the outcomes with respect to peanut allergy prevention in infants introduced to peanut at 4 vs 6 months of age.
    E. There is no need to introduce peanut-containing foods as long as the patient is breastfeeding and the mother consumes peanut-containing foods.

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Allergy Testing and Immunotherapy

Alanna G. Wong, MD,*† Jeanne M. Lomas, DO*†

**Division of Pediatric Allergy/Immunology, Golisano Children's Hospital at Strong, Rochester, NY*

†Division of Allergy, Immunology, and Rheumatology, University of Rochester Medical Center, Rochester, NY

Practice Gaps

General pediatricians should be aware of currently available options for both allergy testing and treatment of allergic disease, including immunotherapy. These are areas that practitioners may have limited exposure to during pediatric training and beyond, thus there are misconceptions about the evaluation and management of various allergic conditions.

Objectives

After completing this article, readers should be able to:

1. Understand when allergy testing is indicated and the different methods used.
2. Recognize what conditions can be treated with allergy immunotherapy and the different modalities currently available for pediatric patients.

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ABBREVIATIONS

EoE	eosinophilic esophagitis
FDA	Food and Drug Administration
IDT	intradermal testing
IgE	immunoglobulin E
SCIT	subcutaneous immunotherapy
SLIT	sublingual immunotherapy
SPT	skin prick testing

GLOSSARY OF TERMS

Aeroallergen Organ Provocation Test – An objective measure of clinical allergy symptoms by applying a known concentration of aeroallergen directly to an area such as the nasal mucosa or conjunctiva.

Anaphylaxis – An immunoglobulin E (IgE)–mediated systemic hypersensitivity reaction typically resulting in immediate and severe symptoms secondary to the immunologic release of mast cell and basophil mediators throughout the body.

Allergen Immunotherapy – A form of treatment that can be given as either sublingual tablets or subcutaneous injections, effective in the long-term management of various allergic diseases (asthma, rhinitis, venom hypersensitivity) by desensitizing patients to clinically relevant allergens over time.

Sensitization – Presence of allergen-specific IgE on allergen exposure, regardless of clinical symptoms.

INTRODUCTION

Atopic diseases in the pediatric population often become a source of major concern for both patients and their caretakers. These conditions are quite common in children, with 5.6% having reported food allergies, 9% with hay fever, 11% with respiratory allergies, and 12% with skin allergies based on the 2012 National Health Interview Survey of US children. (1) Allergies are generally chronic and can significantly affect the child's quality of life. For example, food and venom allergies necessitate carrying an epinephrine autoinjector at all times and limiting exposure whenever possible. This can be burdensome, particularly for adolescent patients. In contrast, some allergens cannot be avoided, such as pollens or dust mites. Exposure to these inhalants may exacerbate allergic asthma or cause persistent symptoms that affect daily functioning and sleep. As such, it is important for general pediatricians to be able to identify and treat atopic disease in children as well as direct patients to specialists for further evaluation and treatment when indicated.

BACKGROUND/HISTORY

Skin testing for allergies was first demonstrated by Charles Harrison Blackley in the late 19th century during experiments regarding the etiology of hay fever. His technique at the time included applying pollen extracts onto abraded skin, with a resulting wheal and surrounding erythema. (2) Percutaneous (or skin prick) testing, currently the most commonly used technique, was first described by Lewis and Grant in 1924. (3) This type of allergy testing became widespread in the 1970s after Pepys modified the technique by using a hypodermic needle. (3) The discovery of immunoglobulin E (IgE) led to the development of the radioallergosorbent test described by Wide et al (4) in 1967 that used radioactive labels. There have been several technical improvements since, including the use of enzyme labels, in modern serum-specific IgE testing. Serum testing is widely used in conjunction with skin testing to detect sensitization to various allergens. (4)

Allergy immunotherapy in humans was first attempted and described by Leonard Noon and later by his colleague John Freeman in 1911. Patients affected by hay fever were injected with grass pollen allergen extracts, and its effects were assessed with conjunctival provocation tests (placing drops of extract into the patient's eyes). This therapy became widespread beginning in the 1950s after clinical trials were performed. (5)

ALLERGY TESTING

There are 2 main forms of testing for immediate (IgE-mediated) allergies: skin testing and serum testing. For contact dermatitis, which is a non–IgE-mediated, delayed-type hypersensitivity reaction, patch testing is often performed in an allergy or dermatology office.

Exposure to the suspected allergen in a supervised clinical setting, such as oral food challenges, medication challenges, and aeroallergen organ provocation challenges, is considered the gold standard for diagnostic allergy testing. (6) However, when considering patient safety and comfort, these options are not always the most practical first step. Allergy skin and serum testing are less time-consuming and more comfortable procedures, with a lower risk of adverse reactions. Challenges can then be performed if appropriate and necessary based on these results.

Skin Prick Testing

Skin prick testing (SPT) is the most common method of testing used by allergists and typically is preferred as an initial approach. It can be performed in patients as young as 1 month of age, when deemed appropriate. (6) Although infants typically exhibit appropriate cutaneous reactivity to antigen, several studies have shown the wheal size produced by SPT to be smaller in this population compared with older (preschool-aged) children and adults. (7)(8)

Also called *percutaneous skin testing,* SPT is performed by placing a desired antigen on the skin (usually the forearm or back, given the sensitivity of the skin in these areas, is preferable). Antigen is available commercially in an aqueous form or is created from fresh foods or medications. Once the extract (or allergen/antigen) is applied, the skin is then punctured to introduce the antigen into the epidermis. Several different instruments can be used in SPT, including hypodermic needles, solid-bore needles, single-headed lancet devices, and multiheaded lancet devices. After 15 to 20 minutes, the resulting wheal diameter and surrounding erythema are measured and compared with controls. Histamine is generally used as the positive control, with saline acting as a negative control. A wheal that exceeds the negative control by 3 mm or more is usually considered positive. The specificity of SPT is 70% to 95% for inhalant allergens and 30% to 70% for food allergens. The sensitivity of SPT is 80% to 90% for inhalant allergens and 20% to 60% for food allergens, and it increases to as high as 90% when fresh foods are used. (9)

Intradermal Testing

Intradermal testing (IDT) involves the injection of an allergen extract intracutaneously. As with SPT, the subsequent wheal and erythema that develop are measured and compared with positive and negative controls. This type of skin testing should be performed only if there is a convincing clinical history with negative SPT results because IDT is more sensitive but less specific. In addition, the risk of a systemic reaction to IDT is higher compared with SPT. Thus, SPT is generally performed first because allergens that are prick positive should not be tested via IDT. (6)(10) It is particularly useful for drug and stinging insect allergy and should not be performed for foods. (9)

Factors that can affect skin test results include cutaneous reactivity, technician performance, and extract potency. The most common cause of false-negative results in skin testing is the use of medications having antihistaminic properties. These medications include first- and second-generation oral antihistamines (including those used for conditions other than allergy, such as cyproheptadine), topical antihistamines (nasal, ocular), and tricyclic antidepressants. Most oral medications with antihistaminic properties should be held for 5 to 7 days before testing, with topical agents held for at least 2 days. Even H_2 antagonists can have some activity in the skin and ideally should be held for 24 hours prior. Table 1 lists common medications that inhibit cutaneous allergy test results (SPT and IDT). Short courses of oral corticosteroids (such as those used for an asthma exacerbation) do not affect test results, although prolonged use of potent topical corticosteroids is discouraged before testing because these may interfere with results. (6)

Serum Testing

Radioallergosorbent testing detects serum IgE antibodies for specific allergens. The average sensitivity compared with SPT has been reported to be approximately 70% to 75%, thus SPT is preferred. (6) Serum testing is favored in certain situations, such as for patients who have diffuse skin disease or who are unable to discontinue the use of suppressive medications before testing. Radioallergosorbent testing is often used in conjunction with SPT to monitor the severity of food allergies and to further determine whether an oral food challenge may be indicated.

For the techniques described thus far, it is important to remember that a thorough clinical history is just as, if not more, important than testing. Positive findings on SPT, IDT, or serum-specific IgE testing indicate only the presence of allergen-specific IgE, and these results alone are not enough to diagnose clinical allergy. Both skin and serum test results may be either false-positive or false-negative. Therefore, positive allergy testing represents sensitization only and not clinical allergy. Based on the combination of a suggestive history and (positive) testing, it is the provider's responsibility to determine whether clinical allergy is present.

TABLE 1. **Common Medications that Inhibit Cutaneous Allergy Testing (Skin Prick and Intradermal Testing)**

MEDICATION	SUPPRESSION OF SKIN TEST RESULTS, D
First-generation H_1 antihistamines	
Chlorpheniramine	1–3
Cyproheptadine	1–8
Diphenhydramine	1–3
Hydroxyzine	1–10
Promethazine	1–3
Second-generation H_1 antihistamines	
Cetirizine	3–10
Fexofenadine	3–7
Loratadine	3–10
Levocetirizine	3–7
Tricyclic antidepressants	
Doxepin	6
Doxepin, topical	11
Imipramine	>10
H_2 antihistamines	
Ranitidine	<1
Leukotriene antagonists	
Montelukast	0
Nasal sprays	
Fluticasone	0
Mometasone	0
Budesonide	0
Azelastine	3–10

Derived from Bernstein IL, Li JT, Bernstein DI, et al; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology. Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol. *2008;100(3)(suppl 3):S1–S148 (6) and Chiriac AM, Bousquet J, Demoly P. In vivo methods for the study and diagnosis of allergy. In: Adkinson NF, Yunginger JW, Bochner BS, et al, eds.* Middleton's Allergy. *8th ed. Philadelphia, PA: Elsevier; 2014:1119–1132. (9)*

INDICATIONS FOR TESTING

As a general principle, allergy testing should be performed only if the results would affect management. If a diagnosis is strongly suspected, confirmatory testing may also be important so that the appropriate counseling and treatment would be offered. For example, if a child has environmental allergies causing severe allergic rhinoconjunctivitis despite multiple medications, and skin or serum testing identifies sensitization to a relevant allergen, avoidance may be advised (such as to animals or dust mites) and allergy immunotherapy could be offered. Alternatively, if the diagnosis is uncertain, testing may be helpful to avoid unnecessary treatment or the possible overlooking of additional etiologies. For example, if a child does not have evidence of an IgE-mediated hypersensitivity to a food, then this food could potentially be reintroduced into the diet and an epinephrine autoinjector may not be indicated.

Environmental Allergens

Skin testing (SPT and occasionally IDT when appropriate) for environmental allergens is useful in patients with chronic seasonal or perennial symptoms of allergic rhinitis or rhinoconjunctivitis, recurrent sinusitis (especially with seasonality), or if there is concern for allergic asthma. However, negative environmental allergy skin testing at a single point in time does not exclude the chance for sensitization in the future because skin test positivity can lag in the pediatric population (especially for children <2 years old), with clinical symptoms preceding positive skin test results. (6)

Food Allergens

Regarding food allergens, skin testing is clearly indicated when an anaphylactic reaction has occurred or symptoms suspicious of an IgE-mediated allergy (hives, intractable vomiting, etc) are demonstrated with ingestion of a specific food. Negative SPT results can be particularly helpful because the tests are highly sensitive, with negative predictive accuracy generally 85% to 95%. (11) Currently, strict dietary avoidance is the mainstay of treatment, in addition to having an epinephrine autoinjector accessible at all times in case of accidental exposure. This is especially important because previous reactions do not predict future symptoms with subsequent ingestions, as many cofactors can play a role during a reaction.

Medication Allergy (Penicillin)

Skin testing for penicillin allergy is well validated and reliable. (6) Penicillin hypersensitivity is the most common self-reported drug allergy and is reported in approximately 10% to 20% of the general population. However, maculopapular and urticarial rashes seen with β-lactam antibiotics given during childhood are more likely due to concurrent viral infection or exanthems and do not necessarily represent an IgE-mediated drug allergy. When the results of both SPT and IDT to penicillin and its major (penicilloyl) and minor (penicilloate) determinants (if available) are negative, tolerance is typically confirmed with an oral medication challenge in the allergist's office. In 2011, one trial specifically looked into pediatric patients with a history of maculopapular or urticarial rash while taking a β-lactam antibiotic. Only 6.8% of the children in that study who were labeled as allergic experienced a reproducible reaction after oral medication challenge with the suspected antibiotic agent within 2 months after initial presentation. Further studies continue to demonstrate this finding, indicating that penicillin allergy is overdiagnosed in this population. (12)(13) In addition, more recent evidence suggests that skin testing may not be necessary in these very-low-risk patients and that a confirmatory graded oral provocation challenge alone is safe and appropriate for many children with a history of mild cutaneous reaction to aminopenicillins. (14) There is a relative lack of evidence regarding validated testing for other agents, and, thus, skin testing is performed with less frequency for classes other than penicillin and is based on the specific situation. Serum IgE testing to penicillin is available but is neither sensitive nor specific and offers little utility in clinical practice. (6) Allergy testing for drugs is exclusively performed for suspected immediate, IgE-mediated hypersensitivity and does not diagnose or exclude the presence of delayed-type hypersensitivity.

Venom Hypersensitivity

Life-threatening systemic reactions secondary to insect stings are estimated to occur in 0.4% to 0.8% of the pediatric population. Children with symptoms limited to the skin (local swelling, flushing, pruritus, urticaria) are considered to be at low risk for a more severe reaction. In particular, for children with large local reactions there is a less than 10% chance of a systemic reaction (usually milder than the index event) and a less than 5% chance of anaphylaxis. Thus, venom testing is not indicated in children with isolated cutaneous symptoms. In contrast, a patient of any age who has experienced a life-threatening systemic reaction after an insect sting should have testing performed because the risk of anaphylaxis with subsequent stings is 30% to 40% in children and immunotherapy to identified insects can dramatically reduce the risk of future systemic reactions. Systemic reactions may present with variable symptoms, ranging from mild to severe with anaphylaxis, including hypotension or the involvement of at least 2 organ systems. Given the high frequency of asymptomatic sensitization, venom testing should not be used for screening purposes. (15)(16)

In children with chronic idiopathic urticaria (>6 weeks of symptoms) with an otherwise unremarkable clinical history, allergy testing is not indicated. Skin or serum IgE testing to search for an etiology rarely yields any answers, and the high rate of false-positives with allergy skin testing can be confusing and of little assistance. (17)

Other Allergic Disease

Allergy testing is sometimes performed for patients with other conditions, such as eosinophilic esophagitis (EoE) or atopic dermatitis (eczema). The former involves tissue infiltration of eosinophils causing chronic inflammation in the esophagus and is thought to be, at least in some patients, a gastrointestinal manifestation of food allergy. Although skin testing may be used in an attempt to identify possible food triggers, EoE is not solely IgE-mediated, and, thus, skin testing to foods is not entirely an accurate test in this setting. (18)(19) There is evidence that food impactions in some patients with EoE occur seasonally and that treatment for environmental allergens (with subcutaneous immunotherapy) reduces the pollen burden, which might also contribute to chronic inflammation, and, in turn, aid in the long-term management of EoE as well as the patient's allergic rhinitis. (20)(21)

Patients with moderate to severe atopic dermatitis that remains uncontrolled despite optimal skin care may also benefit from allergy testing (to both environmental and food allergens) to identify potential triggers. (22) However, caution should be taken in the case of both EoE and atopic dermatitis regarding dietary recommendations made solely based on positive testing. As discussed, false-positives in allergy testing are not rare events, and positive testing to a food in the absence of immediate symptoms indicates sensitization only; it does not confirm clinical allergy. In the case that a food is tolerated regularly in a person's diet without identifiable symptoms, the risk of avoidance in a growing child's diet should be weighed with any potential benefit that elimination from the diet may offer for the underlying atopic disease. It is helpful in these situations to offer a limited trial of dietary avoidance under the care of a registered dietitian to offer alternatives to the foods (or food groups) that are to be avoided.

CONTRAINDICATIONS TO TESTING

Contraindications to allergy skin testing include uncontrolled asthma, diffuse skin rash, current use of antihistaminic medication, pregnancy, and generalized edema. Concurrent use of β-blockers is also a relative contraindication because the symptoms of anaphylaxis may be amplified and the response to epinephrine may be blunted. (6)(23)(24)

ALLERGY IMMUNOTHERAPY

Allergy immunotherapy is indicated for the treatment of patients with allergic rhinitis, allergic conjunctivitis, allergic asthma, or stinging insect hypersensitivity who have clinical symptoms with exposure and also exhibit evidence of specific IgE antibodies on testing. At present, this is the only disease-modifying treatment available for these conditions. Repeated doses of specific allergens are administered with a resulting decrease in the sensitivity of end organs (skin, conjunctiva, nasal mucosa, bronchi). Changes are also noted in the cellular and humoral responses to these allergens. Interestingly, IgE levels for specific allergens actually increase at the start of immunotherapy before steadily decreasing. Thus far, this observed change in IgE has not been shown to strongly correlate with a patient's clinical response to immunotherapy. Thus, repeated skin or serum testing during or after completion of a course of immunotherapy is generally not recommended. There is no lower age limit for allergy immunotherapy, and children as young as 3 years old have been initiated on treatment. (25)

Immunotherapy is currently the only way to build tolerance to an allergen, leading to lasting relief of allergy symptoms in most individuals who complete a 3- to 5-year course. (26) Several studies have demonstrated clinical improvement with this recommended length of therapy even after cessation. One study in particular showed sustained relief 12 years after a 3-year course, although lasting relief varies from patient to patient. (25)(26)(27) There are currently no specific tests or markers that can predict whether a patient will achieve prolonged clinical remission versus relapse after stopping immunotherapy. Thus, clinical evaluation of the patient every 6 to 12 months is recommended to assess for efficacy and tolerance. Duration is tailored to the individual patient, with lack of clinical effect and intolerable adverse effects being the most significant reasons to discontinue therapy.

Although immunotherapy is certainly a time commitment for the patient and the caretaker, the alternative is pharmacotherapy for symptomatic relief that would be continued indefinitely. Some studies have even shown that the cost of a course of immunotherapy is significantly less than the cost of years of medications used to treat the allergic conditions. (26) There are also situations in which the patient continues to have bothersome and persistent symptoms despite proper adherence to medications. In addition, in children, it has been well-established that allergy immunotherapy can have long-term benefits for prevention and treatment of allergic asthma as well. (28)(29) Allergy immunotherapy is generally covered (at least in part) by the patient's health insurance, although prior authorization may need to be obtained for the newer sublingual therapies.

Subcutaneous Immunotherapy

Subcutaneous immunotherapy (SCIT) is the most prevalent and longstanding form of allergy immunotherapy. Gradually increasing doses of allergen extracts are given over time (buildup phase) until the monthly target maintenance dose is achieved. The maintenance dose refers to the therapeutic effective dose. Extracts are derived from allergen source materials and are prepared individually for each patient based on testing results. Technique is important as subcutaneous administration is depended on for proper absorption. An accidental intramuscular injection would result in rapid absorption, with increased risk of a systemic reaction. Injections should be administered in a location under the direct supervision of appropriate medical personnel. The necessary medications and equipment should also be immediately available for the treatment of anaphylaxis, including intramuscular epinephrine. There are various dosing schedules that may be used. Injections are typically initiated at weekly intervals during a conventional buildup phase, eventually reaching a target dose at which maintenance injections can be spaced at monthly intervals. Alternatively, for conditions such as venom hypersensitivity, rush and cluster protocols can shorten the buildup phase, although these carry a significantly greater risk of systemic reactions and have not been well studied in children. (25)(26)

Premedication with an oral antihistamine is advised before each injection to mitigate adverse reactions. Common adverse effects of SCIT include local injection site reactions with large swelling, pruritus, erythema, or pain. These can be treated with supportive measures, including ice, topical corticosteroids, additional oral antihistamines, and nonsteroidal anti-inflammatory drugs or acetaminophen as needed. In previous studies, the frequency of local reactions varies from 26% to 82% of patients treated with SCIT. Due to the possibility of anaphylaxis (<1% of patients receiving conventional SCIT), all patients are asked to remain in the medical office for at least 30 minutes after the injection. Although delayed-onset systemic reactions can occur, life-threatening anaphylaxis outside of the observation time is exceedingly rare. Dosing adjustments are often necessary for reactions and missed doses, especially during the buildup phase given the frequency of injections. Contraindications to SCIT include uncontrolled asthma, inability to communicate clearly to the physician should a reaction occur, concurrent use of β-blockers, and other comorbidities that weaken a patient's ability to survive a systemic allergic reaction. (25) For venom immunotherapy in particular, concurrent use of angiotensin-converting enzyme inhibitors leads to a greater risk of more serious anaphylaxis to a sting. (15)

Sublingual Immunotherapy

Sublingual immunotherapy (SLIT) is a relatively recent therapeutic development that may be more convenient for patients with environmental allergies. Administration of the specific allergen to the oral mucosa is done via fast-dissolving tablets placed underneath the tongue. The medication is taken daily, with the first dose given in the clinic under the direct supervision of appropriate medical personnel. The patient can then continue the remainder of therapy at home, with an epinephrine autoinjector available at all times. Currently in the United States, there are only 4 Food and Drug Administration (FDA)–approved SLIT products available, one of which is approved for ages 5 years and older (Table 2). (25)(34)(35)

Local adverse effects of SLIT include pruritus or swelling of the mouth, tongue, or lip; throat irritation; nausea/vomiting; diarrhea; abdominal discomfort; heartburn; and uvular edema. Most local reactions improve or resolve with repeated use of SLIT, typically in a few weeks or less. Systemic reactions with SLIT are extremely rare. Contraindications include uncontrolled asthma, a history of a severe local reaction to SLIT, a history of a severe systemic reaction to SCIT, as well as known EoE. (34)(35)

Table 3 provides a summary of allergy testing and immunotherapy.

FUTURE DEVELOPMENTS/CONSIDERATIONS

Allergy testing and immunotherapy continue to be fluid areas with ongoing research leading to new developments and improvements in treatment and prevention, especially in the management of food allergy.

One recent development in our understanding of peanut allergy has resulted in a major shift in practice guidelines for general pediatricians. Where previous feeding

TABLE 2. **Food and Drug Administration–Approved Sublingual Immunotherapy (30)(31)(32)(33)**

MEDICATION	APPROVED AGES (Y)
Grastek (Timothy grass)	≥5
Oralair (5-grass mix)	≥10
Ragwitek (ragweed)	≥18
Odactra (house dust mite)	≥18

TABLE 3. **Summary of Allergy Testing and Immunotherapy**

ALLERGY	ALLERGY TESTING GENERALLY RECOMMENDED	IMMUNOTHERAPY AVAILABLE
Food (IgE-mediated)	SPT, serum-specific IgE	No
Environmental (rhinitis, conjunctivitis, asthma)	SPT, IDT, serum-specific IgE	Yes (SCIT, SLIT)
Medication (penicillin, amoxicillin)	SPT, IDT	No
Venom/stinging insect (systemic reaction)	SPT, IDT, serum-specific IgE	Yes (SCIT)

IDT=intradermal testing, SCIT=subcutaneous immunotherapy, SLIT=sublingual immunotherapy, SPT=skin prick testing.

recommendations had been to delay introduction of highly allergenic foods from the infant/toddler diet with the goal to prevent development of food allergy, the LEAP (Learning Early About Peanut Allergy) trial published in 2015 demonstrated the opposite effect regarding peanut. High-risk infants (defined as those with moderate to severe eczema, previously diagnosed egg allergy, or both) randomized to consistent peanut consumption starting within the first 11 months of life (most at approximately 4–6 months of age) had a significantly decreased risk of peanut allergy compared with those who withheld peanut from the diet. Additional studies, including the EAT (Enquiring About Tolerance) trial, have since shown similar effects for early introduction of other highly allergenic foods, although further studies are needed to provide more specific recommendations regarding foods other than peanut. (36) As such, current feeding guidelines have changed to reflect this evidence. Most infants should be fed highly allergenic foods whenever developmentally and culturally appropriate, with emphasis placed on high-risk infants. Infants with severe eczema, already identified or suspected food allergies, or a strong family history of food allergy should be referred to an allergist for further evaluation. They may be candidates for skin or serum IgE testing to foods at 4 to 6 months of age to evaluate appropriateness of early peanut introduction to prevent peanut allergy development. Even when testing is slightly positive, an oral food challenge can be performed in the allergist's office to confirm tolerance. If peanut is introduced successfully without adverse reaction, recommendations are to continue 6 to 7 g per week over at least 3 feedings. Whole peanut should be avoided secondary to risk of choking, but alternate forms to give include thinned peanut butter, Bamba peanut snack, peanut flour, and peanut butter powder. (37)(38)

Oral immunotherapy and epicutaneous immunotherapy for foods is presently being extensively studied in several ongoing clinical trials. This is encouraging because the current treatment for food hypersensitivity is strict avoidance and treatment of accidental ingestions. The results for peanut allergy have been particularly promising, with milk, egg, and fish also being studied. (25)(39)(40)

Regarding environmental allergens, extending the age range for sublingual immunotherapy tablets to include younger patients would certainly be beneficial and is currently being pursued. Applying this modality to other allergens, such as for foods, would also be of interest. Having this be a viable option for younger patients is of particular importance because many children are understandably fearful of injections and, thus, do not pursue treatment.

Allergies, whether secondary to foods, environmental allergens, stinging insects, or medications, can substantially affect the quality of life of pediatric patients. Thoughtful evaluation for pertinent clinical presentations is paramount because both false-positives and false-negatives with testing can lead to unnecessary lifestyle modifications or inappropriate treatment. Management should be a joint effort between the pediatrician and the allergist because these patients and their families require regular monitoring and ongoing education about changing recommendations as new discoveries are made in the field.

Summary

- Based on practice guidelines, skin prick testing is currently the most commonly used method of allergy testing and is the preferred initial approach. (9)
- Long-term symptoms of allergic rhinitis or conjunctivitis, recurrent sinusitis (especially seasonal), or concern for allergic asthma are indications for environmental allergen testing when symptoms are persistent, refractory to standard care, or could be improved by proper allergen avoidance or when patients and families are curious about identifying potential triggers. (6)
- Testing for food allergens is clearly indicated when an anaphylactic reaction has occurred or symptoms suspicious of an immediate, immunoglobulin E (IgE)–mediated allergy are demonstrated with ingestion of a specific food. (6)
- Based on strong evidence, skin testing for penicillin is well validated and reliable. Investigation of penicillin allergy should be performed for any patient with a history of cutaneous reaction to aminopenicillins. (6)(12)
- Based primarily on consensus due to lack of relevant clinical studies and lack of evidence regarding validated testing for other agents, skin testing is performed with less frequency for medication classes other than penicillin.
- Based on practice guidelines, any patient who has experienced a life-threatening systemic reaction after an insect sting should have testing performed, and venom immunotherapy should be considered. Testing is not indicated for reactions limited to the skin in the pediatric population (<16 years of age). (15)(16)
- Based on practice guidelines, allergy immunotherapy is indicated for the treatment of patients with allergic rhinitis, allergic conjunctivitis, allergic asthma, or stinging insect hypersensitivity who demonstrate evidence of specific IgE antibodies with a relevant history and positive testing. (25)
- Subcutaneous immunotherapy consists of injecting gradually increasing doses of allergen extracts over a period (buildup phase) until the monthly target maintenance (therapeutic effective) dose is achieved. (25)(26)
- Sublingual immunotherapy is a relatively recent therapeutic development that may be a more convenient option for patients with environmental allergies. Administration of the specific allergen to the oral mucosa is done via fast-dissolving tablets placed underneath the tongue. (34)(35)

References for this article are at http://pedsinreview.aappublications.org/content/40/5/219.

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1. A 7-year-old boy was referred to a pediatric allergist for evaluation after having several episodes of hives following the consumption of various types of berries, including strawberries, blackberries, and raspberries in various combinations. The allergist advised the family that it is best to start with performing allergy skin and serum testing before proceeding to direct allergen challenge based on which of the following rationales?

   A. Skin and serum testing are considered the gold standard.
   B. Skin and serum testing are less expensive.
   C. Skin and serum testing have a lower risk of adverse reactions.
   D. Direct allergen challenge are less precise.
   E. Direct allergen challenge are valid only for patients older than 12 years.

2. A 12-year-old girl with a history of asthma, allergic rhinitis, and recurrent sinusitis is being evaluated for possible penicillin allergy. She had been taking chronic nasal corticosteroids and loratadine at bedtime for the past 3 months. She was recently admitted to the hospital with asthma exacerbation and was discharged on a 5-day course of oral corticosteroids, which she completed a week ago. She recently had several episodes of sinusitis requiring antibiotic drug courses. Because of suspected penicillin allergy, her antibiotic drug choices have been gradually limited to cephalosporins and macrolides. Which of the following factors will most likely interfere with her skin testing?

   A. Chronic nasal corticosteroid use.
   B. Loratadine use.
   C. Recent episode of asthma exacerbation.
   D. Recent episode of sinusitis.
   E. Recent 5-day course of oral corticosteroids.

3. A 3-year-old boy is brought to the emergency department by emergency medical services after he sustained an anaphylactic reaction to a bee sting while playing outside. The patient was stung over his left cheek. He immediately had diffuse swelling of the left side of his face, diffuse urticarial rash, and acute onset of cough, wheezing, and respiratory distress. The mother called 911, and emergency medical services arrived at the scene in 3 minutes, administered epinephrine, and placed the child on supplemental oxygen. There is no history of bee stings. The family is worried about future similar episodes. In addition to the immediate and acute management, which of the following is the most appropriate in management of this patient to prevent life-threatening reactions to insect envenomation?

   A. Advise the family that a child younger than 5 years is too young for allergy testing and immunotherapy.
   B. Discharge the patient with an epinephrine autoinjection device and consider referral for skin testing if he sustains future bee stings.
   C. Reassure the family that the risk of a life-threatening reaction to insect envenomation is very low and is estimated to be less than 0.1% of the pediatric population.
   D. Recommend venom testing of the 2 older siblings as a screening test.
   E. Refer the patient for immediate skin testing and immunotherapy to reduce the risk of future anaphylaxis.

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4. A 12-year-old girl with a history of seasonal allergies and asthma is seen in the allergy clinic during her spring break for follow-up. She was diagnosed as having asthma at 4 years of age and had multiple exacerbations primarily triggered by seasonal changes and environmental allergens. She is well-controlled on daily inhaled corticosteroids and takes β_2 agonists by inhaler as needed for exacerbations. She also takes antihistamines almost daily during high pollen count blooming season. Because she has not shown signs of outgrowing her asthma, allergy skin testing is being considered. Which of the following is a contraindication to allergy skin testing in this patient?

   A. Allergic rhinitis.
   B. Current daily use of antihistamines.
   C. Current daily use of inhaled corticosteroids.
   D. No contraindications to allergy skin testing.
   E. Occasional use of β_2 agonists.

5. The patient in the vignette in question 4 was scheduled to come back for allergy skin testing in the summer season. Her skin testing was positive for several environmental allergens. She is to be started on immunotherapy. Which of the following is the optimal duration of allergy immunotherapy required to obtain a sustained response?

   A. 6–12 months.
   B. 1–2 years.
   C. 3–5 years.
   D. 5–10 years.
   E. Lifelong.

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Immunodeficiency Disorders

Ivan K. Chinn, MD,[*,†] Jordan S. Orange, MD, PhD[‡,§]

Department of Pediatrics, Section of Immunology, Allergy, and Rheumatology, Baylor College of Medicine, Houston, TX
[†]*Center for Human Immunobiology, Texas Children's Hospital, Houston, TX*
[‡]*Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, NY*
[§]*New York Presbyterian Morgan Stanley Children's Hospital, New York, NY*

Education Gaps

Immunodeficiencies are no longer considered rare conditions. Although susceptibility to infections has become well-recognized as a sign of most primary immunodeficiencies, some children will present with noninfectious manifestations that remain underappreciated and warrant evaluation by an immunologic specialist. Providers must also consider common secondary causes of immunodeficiency in children.

Objectives

After completing this article, readers should be able to:

1. Recognize infectious signs and symptoms of primary immunodeficiency that warrant screening and referral to a specialist.
2. Understand noninfectious signs and symptoms that should raise concern for primary immunodeficiency.
3. Determine appropriate testing for patients for whom immunodeficiency is suspected.
4. Discuss the management of patients with primary immunodeficiency.
5. Appreciate secondary causes of immunodeficiency.

AUTHOR DISCLOSURE Dr Chinn has disclosed that he is the recipient of a Translational Research Program grant from the Jeffrey Modell Foundation. Dr Orange has disclosed that he is a consultant on the topic of therapeutic immunoglobulin for Shire, CSL Behring, and Grifols and that he serves on the scientific advisory board for ADMA Biologics. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ALC	absolute lymphocyte count
ALPS	autoimmune lymphoproliferative syndrome
CGD	chronic granulomatous disease
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
Ig	immunoglobulin
PID	primary immunodeficiency
SCID	severe combined immunodeficiency disease
SLE	systemic lupus erythematosus
TLR	toll-like receptor

INTRODUCTION

Immunodeficiency disorders represent defects in the immune system that result in weakened or dysregulated immune defense. These deficiencies may occur as primary diseases or secondary conditions. This article reviews primary and secondary immunodeficiencies, with particular emphasis on the evaluation and management of children with primary immunodeficiencies (PIDs).

PRIMARY IMMUNODEFICIENCIES

PIDs constitute inherent defects in immunity, most of which arise from inborn deviations in the genetic code. More than 300 PIDs have been identified. These conditions have been placed into 9 categories corresponding with their clinical and immunologic phenotypes by an international group of experts who evaluate these diseases every 2 years (Table 1). (1) Although PIDs were previously believed

TABLE 1. **Primary Immunodeficiency Categories (1)**

1. Immunodeficiencies affecting cellular and humoral immunity
2. Combined immunodeficiencies with associated or syndromic features
3. Predominantly antibody deficiencies
4. Diseases of immune dysregulation
5. Congenital phagocytic defects
6. Defects in intrinsic and innate immunity
7. Autoinflammatory disorders
8. Complement deficiencies
9. Phenocopies of PIDs

to represent rare conditions, they are now known to affect 1 of every 1,200 to 2,000 individuals, with growing prevalence due to increased recognition. (2)(3) The magnitude of this disease frequency, therefore, mandates that all health-care providers recognize the associated clinical infectious and noninfectious characteristics, testing options, and management recommendations for children with PIDs. And because so many PIDs present in childhood, and several are now captured by newborn screening, their understanding by pediatricians remains especially important.

Infectious Signs and Symptoms of PID

Infections serve as the key hallmark warning signs for the presence of PID. (4) In general, children with PIDs develop infections more frequently, more severely, and more atypically. Although noninfectious characteristics of PIDs can result from inappropriate immune function and are discussed in the next section, the link between PID and infection remains essential and must be regarded as a prompt to consider PID in pediatric practice. Each of the 9 PID categories conveys a different risk for certain infectious susceptibilities in accordance with the molecular mechanism for the impaired immunity. Offending organisms encompass the entire spectrum of pathogens, including bacteria, viruses, fungi, and parasites. Thus, awareness of infections associated with defective humoral immunity, T-cell function, phagocytic capacity, complement activity, and other innate immunity becomes essential.

Defects in humoral immunity that cause PID result in impaired antibody production. Infants receive maternal immunoglobulin (Ig) G transplacentally. Because the half-life of IgG is approximately 21 days in the circulation, children have protection from these maternal antibodies until approximately 3 to 4 months of life. At that time, characteristic infections tend to ensue, although some antibody deficiencies are known to present at older ages. Because antibodies serve as critical elements for protection of the sinopulmonary tract, affected individuals typically develop recurrent otitis media, sinusitis, and pneumonia. Infections are by no means limited to these sites, however, and can result in sepsis, meningitis, osteomyelitis, or chronic diarrhea. For example, X-linked agammaglobulinemia is characterized by a lack of B cells due to mutations in *BTK* located at Xq22.1. Absence of B cells results in failure to produce IgG, IgA, IgM, and IgE. In affected boys, disappearance of maternal antibodies is associated with the appearance of recurrent sinopulmonary tract infections, classically by polysaccharide-encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. (5) The lack of antibodies also results in susceptibility to infections by mycoplasmal and pseudomonal organisms, *Salmonella* species, *Campylobacter jejuni*, rotavirus, and *Giardia lamblia*.

T-cell deficiency produces combined humoral and cellular immune defects. Because of this extensive effect on immune function, affected individuals demonstrate susceptibility to opportunistic fungal, viral, mycobacterial, and parasitic infections in addition to the infections observed in antibody deficiencies. Classic pathogens include candidal species, *Pneumocystis jirovecii*, *Mycobacteria* species (including bacille Calmette-Guérin), and *Cryptosporidium parvum*. Viral infections surpass the ordinary and are notably severe, disseminated, or persistent. Severe combined immunodeficiency disease (SCID) serves as a classic example of primary T-cell deficiency. The diagnosis is established by either 1) the absence or a very low number of T cells (<300 $CD3^+$ T cells/mm^3) with no or very low T-cell function ($<10\%$ of the lower limit of normal) as determined by response to phytohemagglutinin or 2) the presence of T cells of maternal origin. (6) Mutations in at least 16 genes lead to SCID, and most forms are caused by disrupted T-cell development secondary to abrogated T-cell receptor formation or cytokine signaling (Table 2). (1) The most common type of SCID in the United States results from mutations in *IL2RG* at Xq13.1 and is, thus, found in boys. SCID represents a true pediatric emergency, and mortality from infections is certain if affected infants are not treated appropriately. (7) Life-threatening infections are caused by respiratory syncytial virus, rhinovirus, parainfluenza virus, adenovirus, cytomegalovirus, and even attenuated vaccine strains of measles virus, varicella virus, rotavirus, and oral poliovirus. Invasive bacterial and fungal infections also occur, the former mostly resulting from impaired humoral immunity secondary to the defects in T-cell immunity.

TABLE 2. **Causes of Severe Combined Immunodeficiency Disease**

ASSOCIATED GENE	LYMPHOCYTE PHENOTYPE	DEFECTIVE MECHANISM
IL2RG	$T^-B^+NK^-$	Signaling for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21
JAK3	$T^-B^+NK^-$	Same as *IL2RG*
RAG1	$T^-B^-NK^+$	Formation of T- and B-cell receptors
RAG2	$T^-B^-NK^+$	Same as *RAG1*
DCLRE1C	$T^-B^-NK^+$	Same as *RAG1*
PRKDC	$T^-B^-NK^+$	Same as *RAG1*
LIG4	$T^-B^-NK^+$	Same as *RAG1*
NHEJ1	$T^-B^-NK^+$	Same as *RAG1*
IL7R	$T^-B^+NK^+$	Signaling for IL-7
PTPRC	$T^-B^+NK^+$	Receptor signaling and T-cell activation
CD3D	$T^-B^+NK^+$	T-cell receptor signaling
CD3E	$T^-B^+NK^+$	Same as *CD3D*
CD247	$T^-B^+NK^+$	Same as *CD3D*
CORO1A	$T^-B^+NK^+$	Same as *CD3D*
AK2	$T^-B^-NK^-$	Stem cell maturation
ADA	$T^-B^-NK^-$	Lymphocyte survival

IL=interleukin.

Because neutrophils play a significant role in the clearance of bacterial and fungal pathogens, PIDs due to defective phagocytic capacity are marked by infections caused by these organisms. Phagocytic impairment can result from inadequate neutrophil quantity or function. Classic infections in children with neutrophil deficiency include skin or solid organ abscesses, cellulitis, pneumonia, sepsis, and severe gingivitis or periodontitis. Other signs of a phagocytic defect include omphalitis, poor wound healing, and aphthous stomatitis. Affected individuals have an increased risk of life-threatening infections from *Staphylococcus aureus* and *Pseudomonas aeruginosa*. As a key illustration, chronic granulomatous disease (CGD) serves as an example of PID caused by impaired neutrophil function. This condition arises from defects in components of nicotinamide adenine dinucleotide phosphate oxidase, which produces the oxidative burst needed for neutrophils to kill phagocytized organisms. (8) The most common form of CGD results from mutations in *CYBB*, which is located at Xp21.1-p11.4. Thus, most children with CGD are boys. CGD can be recognized by susceptibility to catalase-positive organisms, such as *S aureus*, *Serratia marcescens*, *Klebsiella* species, *Burkholderia cepacia*, *Aspergillus* species, and *Nocardia* species (8)(9) Infections caused by unusual pathogens, especially methylotrophic microorganisms capable of using single-carbon compounds as their sole source of energy, should also raise concern for the presence of CGD. (10) In children with CGD who have received bacille Calmette-Guérin immunization, infection by the bacterium itself should be considered. Characteristic sites of various infections in CGD include the skin, lungs, lymph nodes, liver, spleen, central nervous system, and bones.

Children with defects in primary complement deficiencies can be recognized by infections caused by encapsulated bacteria. (11) Complement deficiency, whether of the early or terminal classical complement pathway components, should be considered in children who have invasive meningococcal disease, such as sepsis or meningitis from *Neisseria meningitidis*. Individuals who have primary early classical complement pathway protein (C1, C4, C2, and C3) deficiencies further demonstrate susceptibility to other encapsulated bacteria, such as *S pneumoniae* and *H influenzae*.

Finally, children with PIDs due to other defects in innate immunity exhibit susceptibility to a variety of pathogens, depending on the critical defense mechanism affected. For example, natural killer cell deficiency should be suspected in individuals with recurrent, unusual, or severe herpesviral infections. (12)(13) Children with defects in the interferon-γ–interleukin-12 signaling pathway, on the other hand, develop atypical mycobacterial infections. (14) Perturbation of other key innate immune signaling pathways leads to chronic mucocutaneous candidiasis, which should be suspected in children with thrush that is unusually recurrent or unresponsive to nystatin. (15) Finally, defects in toll-like receptor (TLR) signaling pathways offer an excellent example of the diversity of infectious susceptibilities affected by various innate immunity disorders. Humans express 10 TLRs, each of which performs an inherent danger-sensing function by recognizing specific intracellular or extracellular bacterial, fungal, or viral components. TLR3 deficiency leads to susceptibility to herpes simplex virus encephalitis. (16) IRAK-4 and MyD88, however, serve as adaptor molecules that mediate signaling downstream from all the other TLRs (except partly TLR4). Deficiencies of either of these proteins result instead in vulnerability to invasive infections (sepsis, meningitis, arthritis, and osteomyelitis, among others) that are caused by pyogenic bacteria, such as *S aureus*, *S pneumoniae*, and *H influenzae*, rather than by viruses or fungi. (17)

Noninfectious Signs and Symptoms of PID

Improved understanding of PIDs and enhanced diagnostic capabilities, especially genetic testing, (18) have provided greater awareness of the need to appreciate noninfectious manifestations, as discussed in the following paragraphs, that can serve as early or initial warning signs for the presence of underlying PID. The pediatrician should keep in mind that inherently defective immunity not only results in an inability to defend against the external environment (ie, infections) but also produces impaired ability to navigate the internal environment, leading to autoimmune and autoinflammatory conditions. In some children, these conditions will appear before infections ensue and can engage nearly any organ system. Affected children may, therefore, first come to the attention of other specialist providers. Presence of any of these features in a pediatric patient, especially with early or very early onset, should prompt consideration of additional evaluation for underlying PID. These noninfectious manifestations of PIDs are reviewed in the following accompanying tables and figures. Of importance, the lists of defective PID genes provided in the tables and figures are by no means comprehensive. Instead, they are intended to underscore the degree to which concern for PID is deserved.

Gastrointestinal disorders can reveal the presence of underlying PID (Table 3). (19) Autoimmune enteropathy can be observed when children lack regulatory T cells. The autoimmune disease in other PIDs, on the other hand, leads to inflammatory bowel disease. In several PIDs, dysregulated inflammation rather than autoimmunity results in inflammatory bowel disease. Finally, the presence of intestinal inflammation with bowel atresias is nearly uniquely associated with *TTC7A* deficiency. Thus, children with chronic enteropathy, inflammatory bowel disease, or multiple intestinal atresias should all be considered for evaluation for underlying PID.

A variety of dermatologic conditions, many of which relate to underlying dysregulated immunity in the skin, can signal the existence of PID (Fig 1). (20) Eczema is a presenting feature of several PIDs, most notably hyper-IgE syndrome and Wiskott-Aldrich syndrome. Neutrophilic pustular dermatosis, or Sweet syndrome, can be observed in proteasome-associated autoinflammatory syndromes. (21) Ectodermal dysplasia, on the other hand, can suggest PID due to a defect in nuclear factor kappa-light-chain-enhancer of activated B cells signaling or store-operated calcium entry. Cutaneous granulomas have been associated with CGD, ataxia-telangiectasia, and Blau syndrome in addition to several other PIDs. Abnormal hair can also serve as a sign of PID. Hypopigmented hair is observed in Chédiak-Higashi, Griscelli, and Hermansky-Pudlak syndromes, and thin or sparse hair is present in cartilage-hair hypoplasia and dyskeratosis congenita. Brittle hair due to trichorrhexis invaginata, so-called bamboo hair, is essentially pathognomic for Comèl-Netherton syndrome. Meanwhile, the complete absence of hair (alopecia totalis) should engender concern for *NFKB2* or *FOXN1* deficiency. Familial cold autoinflammatory syndrome is marked by a phenotype of cold-induced urticaria (as characterized by a wheal and flare response to an ice cube placed on the skin) and is caused by mutations in

TABLE 3. **Gastrointestinal Manifestations of PIDs**

NEARLY 40 PID GENES ARE ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE OR NONINFECTIOUS ENTEROPATHY
ADAM17, AIRE, ARPC1B, BACH2, CD40LG, CD55, CTLA4, CYBA, CYBB, DKC1, DOCK8, FOXP3, IKBKG, IL10, IL10RA, IL10RB, IL2RA, ITCH, LRBA, MALT1, MVK, NCF1, NCF2, NCF4, NEIL3, NFAT5, NLRC4, NOD2, PIK3CD, PLCG2, STAT1, STAT3, STXBP2, TNFAIP3, TTC37, TTC7A, WAS, XIAP, ZBTB24

PID=primary immunodeficiency.

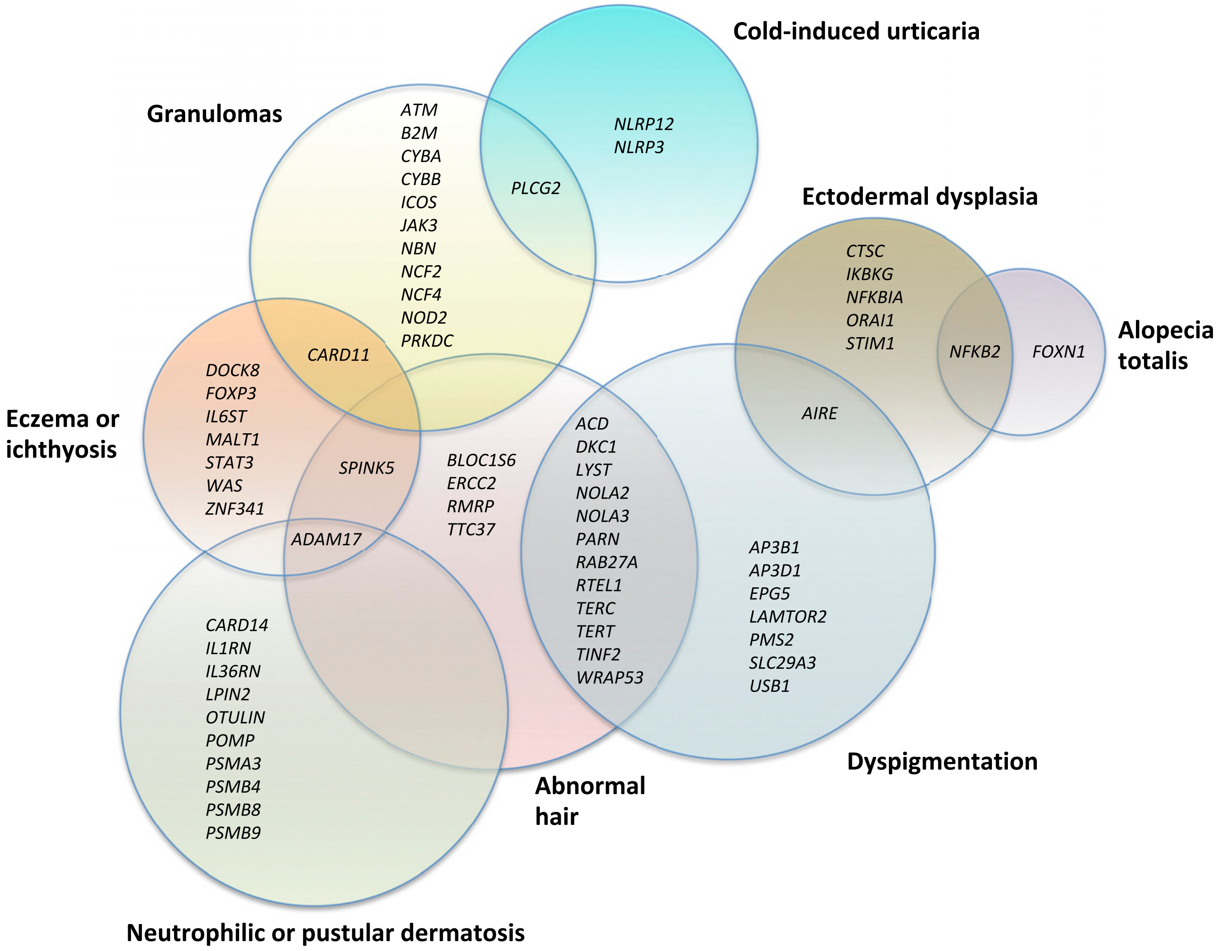


Figure 1. Dermatologic manifestations of primary immunodeficiencies.

NLRP3 or *NLRP12*. A different form of cold-induced urticaria that produces a negative ice cube test but significant wheal responses to evaporative cooling occurs in PLCγ2-associated antibody deficiency and immune dysregulation. Finally, abnormal skin pigmentation can be found in several PIDs, including dyskeratosis congenita (reticular hyperpigmentation) and Chédiak-Higashi, Griscelli, or Hermansky-Pudlak syndromes (hypomelanosis or albinism).

Because PIDs are caused by deficient and dysregulated immunity, it comes as little surprise that some affected individuals will present with autoimmune disease as the chief or even sole manifestation (Fig 2). (22)(23)(24) Noninfectious arthritis, including juvenile idiopathic arthritis, may be a sign of a hyperinflammatory PID condition. Autoimmune cytopenias are classically associated with impaired immunologic tolerance, whether through defective negative selection of T cells in the thymus or decreased regulatory T-cell inhibition of autoreactive T cells. (25) They can also present in individuals with autoimmune lymphoproliferative syndrome (ALPS). Vasculitis serves as a feature of many of the periodic fever syndromes and several complement deficiencies. In terms of periodic fever syndromes, the known associated features underscore the need to consider further evaluation in a child who develops fevers of regular chronicity, arthritis, or vasculitis, and any other signs of inflammation. Most of these syndromes result from hyperactivation of inflammasomes, which are protein complexes critical for inducing inflammatory responses, and can be treated with targeted biological modifiers. (26) Vasculitic disease is also known to occur in several newly described PIDs. Thus, it seems likely that novel PIDs will continue to be discovered as causes of vasculitis in children. Finally, evaluation for PIDs should be considered for children who present with systemic lupus erythematosus (SLE) or SLE-like disease. SLE is known to be associated with deficiencies of almost all components of the classical complement pathway (except C9). Individuals with CGD and ALPS can also present with SLE-like features. It remains important to note that variants of the disease known as hemophagocytic lymphohistiocytosis (HLH) can present with an

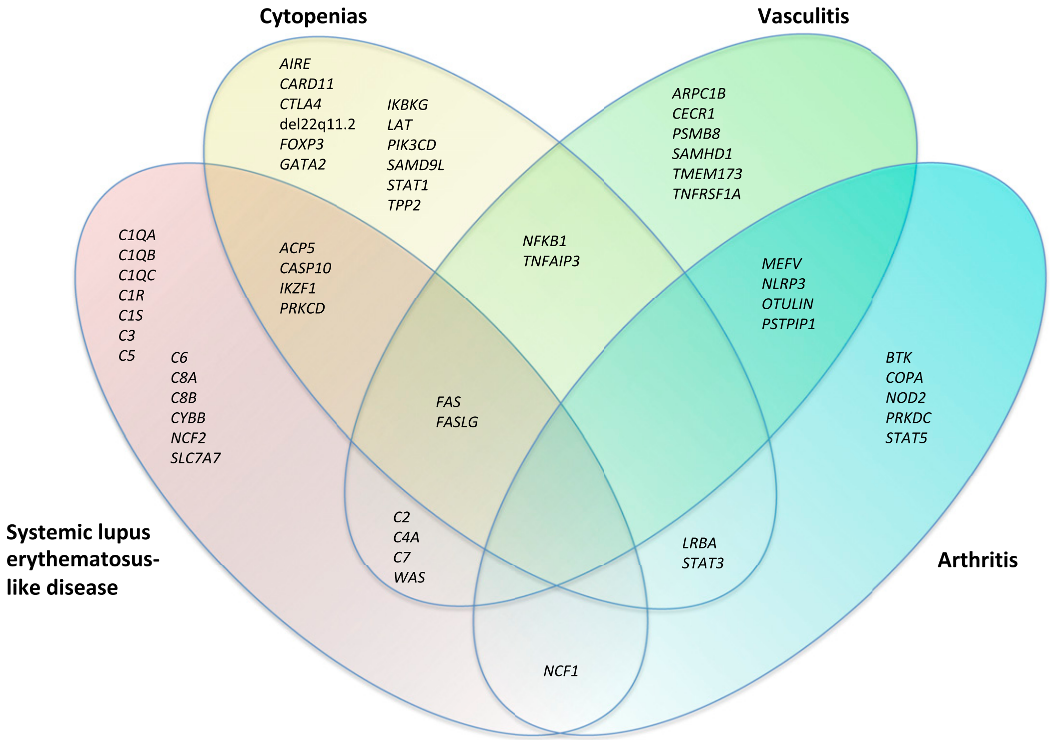


Figure 2. Autoimmune manifestations of primary immunodeficiencies.

inflammatory syndrome known as macrophage activation syndrome. This condition must be recognized appropriately because it is treated more like HLH than other inflammatory conditions that the symptoms might mimic.

Screening for PIDs should be strongly considered in children with early-onset endocrinopathies (Fig 3). Most of these endocrine disorders are autoimmune, resulting from the disrupted tolerance mechanisms inherent to the associated PIDs. Severe or difficult-to-control type 1 diabetes can indicate regulatory T-cell dysfunction. Primary adrenal insufficiency is an archetypal feature of *AIRE*, *MCM4*, and *NFKB2* deficiencies. Hypoparathyroidism is observed in *AIRE* deficiency and DiGeorge anomaly. In fact, the association between neonatal hypocalcemia and DiGeorge anomaly remains well appreciated. Clinicians must realize that the absence of 22q11.2 hemizygosity does not exclude the diagnosis of DiGeorge anomaly, as nearly half of affected individuals may not have the characteristic deletion. (27) Children who present with any features (eg, hypocalcemia or hypoparathyroidism, congenital cardiac disease, or developmental or neuroanatomical defects) characteristic of DiGeorge anomaly should, therefore, be evaluated for potential thymic dysfunction. Growth hormone deficiency represents a classic characteristic of *STAT5B* deficiency but is additionally known to occur in patients with *NFKB2* deficiency and ataxia-telangiectasia. Finally, thyroid disease seems underappreciated as a manifestation of PID but can provide a clue to the existence of underlying PIDs.

Two important hematologic/oncologic conditions should raise concern for underlying PIDs (Table 4). The PID mechanisms that lead to these 2 disorders include impaired control of immunologic activation and dysregulated proliferation of immune cells. First, lymphoproliferative disease suggests an inherent defect in immune function. For example, in ALPS, abnormal proliferation of immune cells occurs due to defective apoptosis. Meanwhile, several other PIDs are characterized by lymphoproliferative disease associated with Epstein-Barr virus infection. Lymphoid hyperplasia is observed in autosomal recessive hyper-IgM syndromes. Second, pediatric patients who develop HLH should be screened for PIDs if they do not have defects in any of the familial HLH genes. (28)(29) PIDs associated with HLH include Chédiak-Higashi, Griscelli, and Hermansky-Pudlak syndromes; CGD; periodic fever syndromes; and a variety of other conditions that affect cytotoxic T-cell or natural killer cell function.

Several PIDs are characterized by neurologic signs (Fig 4). (30) These abnormalities occur most typically due to roles that the damaged genes would normally serve outside of the immune system. That said, the precise mechanism for ataxia and hearing loss remains unclear in many conditions and is often not directly related to the defective

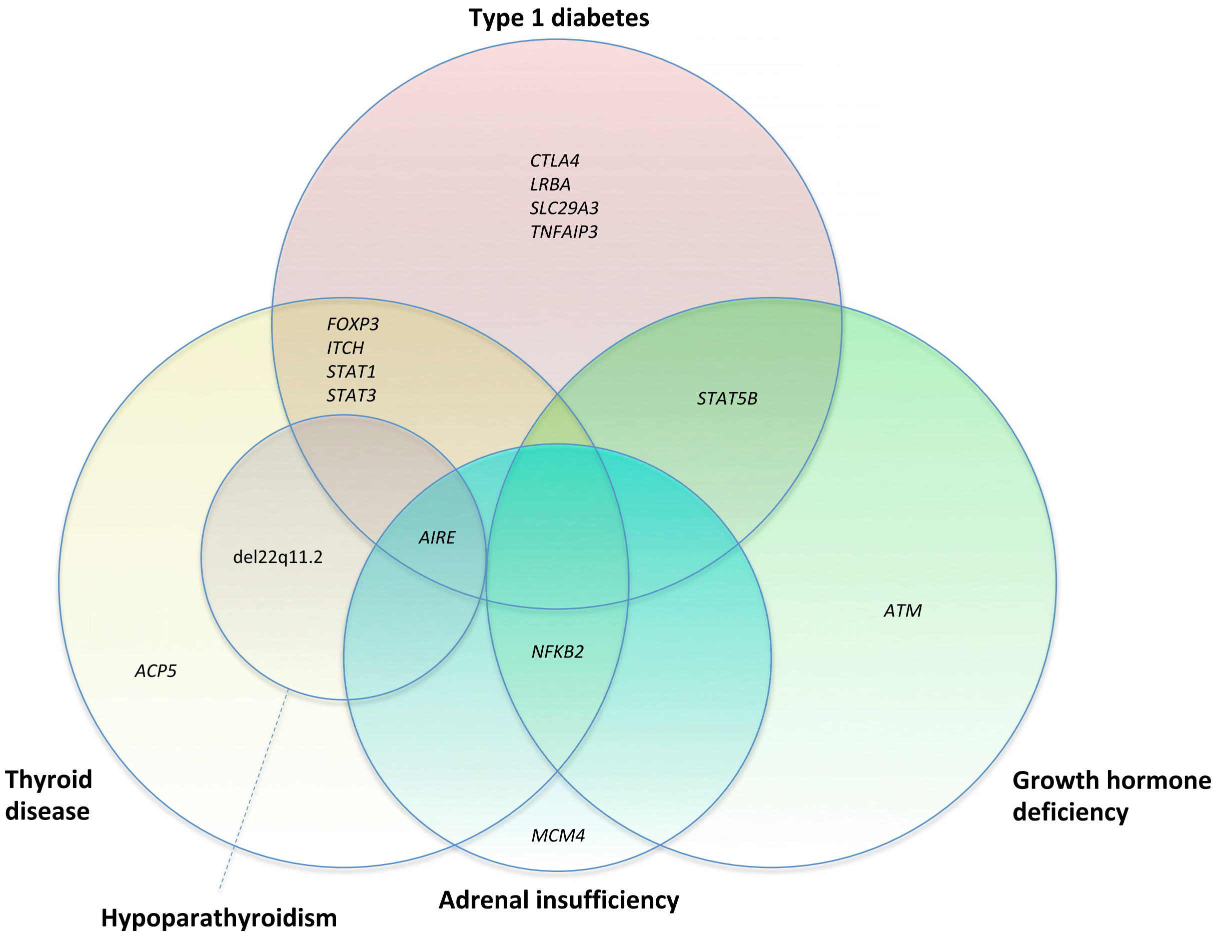


Figure 3. Endocrinologic manifestations of primary immunodeficiencies.

immune function in the associated PID. Ataxia is a typical feature of ataxia-telangiectasia, Chédiak-Higashi syndrome, and Hoyeraal-Hreidarsson syndrome, among others. Hearing loss, on the other hand, is a fundamental attribute of Carnevale-Mingarelli-Malpuech-Michels syndrome, Muckle-Wells syndrome, H syndrome, and other PIDs. Next, developmental delay is clearly associated with a variety of PIDs, but providers often neglect to evaluate for defective immunity due to the attention given to the neurologic deficits. This association emphasizes the critical intersection between neurologic development and activity and immune function, especially in terms of preservation of DNA integrity. Double-stranded break DNA repair seems to play an essential role in cognitive development, and children with PIDs caused by a defect in this repair mechanism present with developmental delay. As another example, developmental delay is observed in immunodeficiency–centromeric instability–facial anomalies syndrome, which is caused by aberrant

TABLE 4. **Hematologic/Oncologic Manifestations of PIDs**

CONDITION	ASSOCIATED PID GENES
Lymphoid hyperplasia or lymphoproliferative disease	*AICDA, CASP8, CASP10, CD27, CD70, CECR1, CTLA4, FAAP24, FAS, FASLG, ITK, LAT, LRBA, MAGT1, MVK, PIK3CD, PIK3R1, PRKCD, RASGRP1, RBCK1, SH2D1A, SLC29A3, STAT3, STAT5B, STK4, TPP2, UNG, XIAP*
Hemophagocytic lymphohistiocytosis	*AP3B1, ATM, BTK, CARMIL2, CD27, CD3E, CYBA, CYBB,* del22q11.2, *DKC1, FAS, IKBKG, IL2RG, IL7R, ITK, LYST, MAGT1, MEFV, NCF1, NLRC4, ORAI1, PIK3CD, PRF1, RAB27A, RAG1, RAG2, SH2D1A, STAT1, STAT2, STAT3, STX11, STXBP2, TNFRSF1A, UNC13D, WAS, XIAP*

PID=primary immunodeficiency.

DNA methylation and chromatin structure. Other examples of developmental delay and PID caused by inappropriate processing of nucleic acids include *ADAR*, *CHD7*, *SMARCAL1*, and *TRNT1* deficiencies. Aside from defects in nucleic acid handling, glycosylation is also known to play a vital role in immunologic and neurologic processes. As a result, a variety of congenital disorders of glycosylation represent PIDs that manifest as developmental delay. Last, unidentified DiGeorge anomaly should always be considered in a child with neurocognitive deficits, behavioral issues, or various psychiatric disorders. (31) Thus, clinicians should be aware of these neurologic associations and consider immunologic evaluation accordingly.

Several rare noninfectious pulmonologic conditions can suggest the presence of underlying PIDs (Table 5). Interstitial lung disease has been reported in several PIDs. Pulmonary alveolar proteinosis is most commonly associated with *CSF2RA* deficiency but can also be observed in patients with other PIDs. Pulmonary capillaritis and hemorrhage should raise concern for *COPA* syndrome. Finally, eosinophilic pneumonia represents a key feature of lung disease, immunodeficiency, and chromosome breakage syndrome caused by *NSMCE3* deficiency.

Finally, clinicians should be aware of 2 additional noninfectious manifestations of PIDs (Table 6). First, allergies, which are often severe or directed toward numerous agents, can serve as the presenting feature of several PIDs. In many of these conditions, the atopy is accompanied by markedly elevated serum IgE levels. Second, skeletal dysplasia serves as a classic feature of spondyloenchondrodysplasia with immune dysregulation, cartilage-hair hypoplasia, and Schimke immuno-osseous dysplasia but can denote the presence of other PIDs as well.

When to Test for PID

The decision of when to test for or refer a child for evaluation of a suspected PID may be affected by several factors.

First, a history of recurrent, severe, or unusual infections or any of the noninfectious issues discussed previously herein merits immunologic evaluation. The definition of

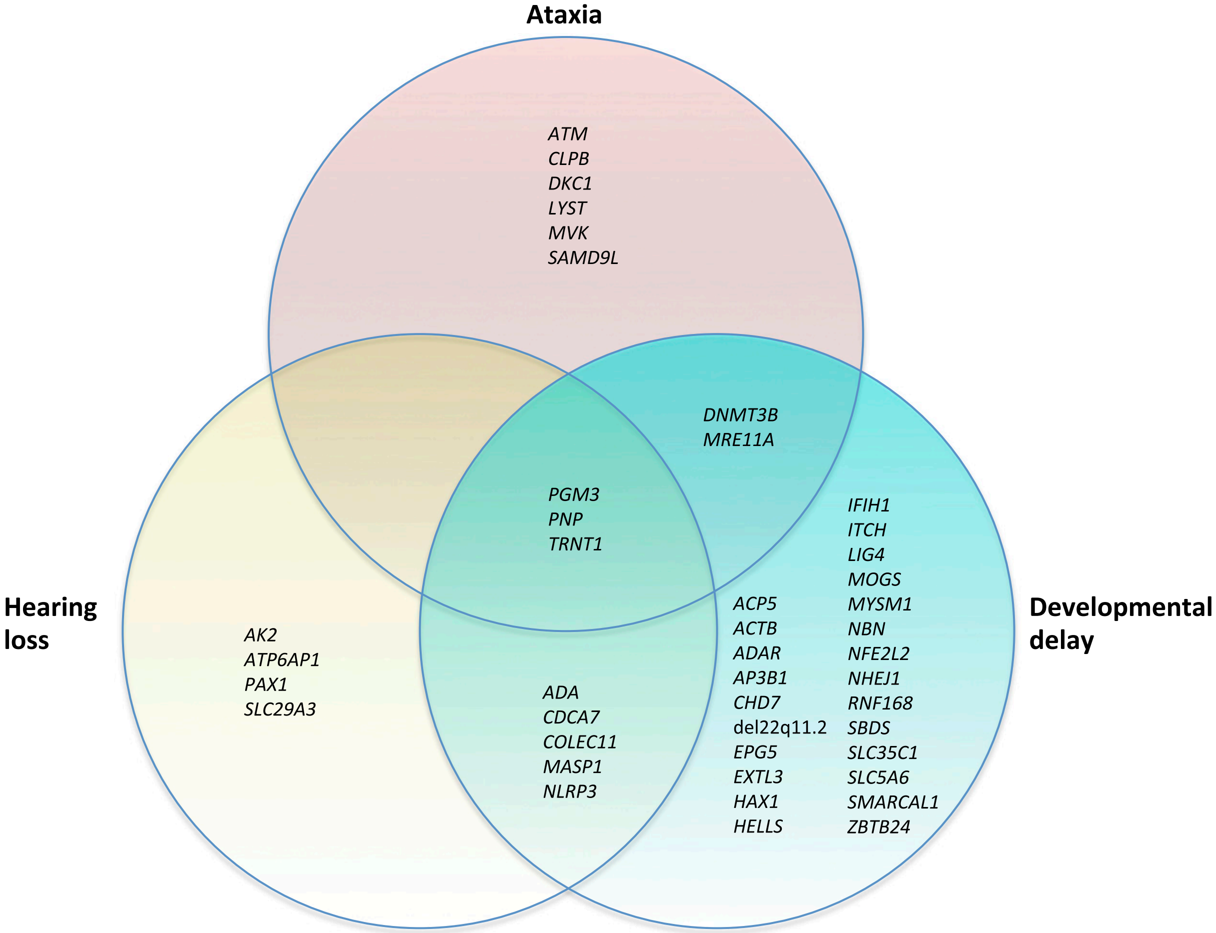


Figure 4. Neurologic manifestations of primary immunodeficiencies.

TABLE 5. Pulmonologic Manifestations of PIDs

CONDITION	ASSOCIATED PID GENES
Interstitial lung disease	*COPA, ITCH, STAT3, TMEM173, TNFAIP3, XIAP*
Pulmonary alveolar proteinosis	*CD40LG, CSF2RA, GATA2, SLC7A7*
Capillaritis and hemorrhage	*COPA*
Eosinophilic pneumonia	*NSMCE3*

PID=primary immunodeficiency.

recurrent remains imprecise. It may not be unusual (17% incidence rate) for a 1-year-old child to have had 3 or more episodes of otitis media, and almost half of the children will have had at least 3 occurrences of otitis media by 3 years of age. (32) One large study suggests that healthy children younger than 3 years may have 11 respiratory tract infections per year, and healthy children aged 3 to 5 years may have 8 respiratory tract infections annually. (33) Thus, clinical judgment remains necessary. As a general rule of thumb, it is the clinical practice of the authors to advise pediatricians to consider PID in their patients who distinguish themselves from the general patient population regarding the occurrence of infections. Statistically speaking, a pediatric practice of 10,000 patients will have 5 to 10 cases of PID overall. Pediatricians should, therefore, be mindful of patients who exist as outliers from an infectious standpoint so that they will be sure to capture PID cases within their practice.

Second, the family history may encourage immunologic testing. Underlying PID should be considered if family members have had recurrent or unusual infections, especially maternal uncles or other males. Other suspicious elements of the family history include consanguinity and early childhood mortality from infections or unexplained causes.

TABLE 6. Other Noninfectious Manifestations of PIDs

CONDITION	ASSOCIATED PID GENES
Allergies	*CARD11, CARMIL2, CTLA4, DOCK8, FOXP3, PGM3, SPINK5, WAS, WIPF1*
Skeletal dysplasia	*ACP5, ADA, ALG12, EXTL3, NBAS, PGM3, RNU4ATAC, RMRP, SMARCAL1*

PID=primary immunodeficiency.

Third, investigation for PID may be warranted in children with physical examination findings consistent with any of the noninfectious presentations mentioned. Children with failure to thrive should also raise suspicion for underlying PID. Furthermore, a child who demonstrates absent or minimal lymphatic tissue should unquestionably be assessed for an underlying PID.

Finally, infants with abnormal newborn screening tests for SCID must receive immunologic evaluation. As of the end of 2017, all but 2 states (Louisiana and Indiana) have implemented active SCID newborn screening programs. The screening test is designed to detect absent or low numbers of T-cell receptor excision circles in blood spots from Guthrie cards. (34) Thus, an abnormal newborn screening test may signify the presence of T-cell deficiency.

Laboratory Testing for PID

Several tests are recommended for initial evaluation for suspected PID. First, because defects in humoral immunity predominate, (3)(35) quantitative measurement of serum immunoglobulin levels and functional assessment of specific antibody responses provide excellent screening tests for PID. Specific antibody function should be tested by determining antibody production toward immunizations. (36) These functional activities represent the most standardized, most uniform, and best-studied humoral immune responses. As a more advanced diagnostic intervention, children older than 2 years can be additionally tested for humoral responses to the polysaccharide antigens in the 23-serotype pneumococcal polyvalent vaccine. Overall, these investigations are performed by obtaining baseline antibody titers, administering the relevant vaccine, and measuring the postimmunization titers (eg, approximately 3 weeks after immunization for tetanus toxoid; both 4 to 8 weeks and 6 months after immunization for the 23-serotype pneumococcal polyvalent vaccine). Next, a complete blood cell count with a manual differential count can be used to screen for quantitative T-cell deficiency through the absolute lymphocyte count (ALC). In a newborn, an ALC less than $2,500/\mu L$ ($<2.5 \times 10^9/L$) suggests that T cells have not developed fully and that they may even be absent in whole or in part. (37) From a PID perspective, it is essential for pediatricians to focus on and calculate the ALC in routine blood cell counts. Any abnormalities should be followed by a T-cell subset analysis performed by flow cytometry to ensure the appropriate presence and distribution of the different subpopulations. Absence of a cardiothymic silhouette on chest radiographs in an infant should also raise concern for the absence of T cells. For functional assessment of T cells, in vivo delayed-type hypersensitivity testing by the intradermal injection of T-cell antigens such as tetanus toxoid and *Candida albicans* can be performed in the office setting, but the recommended option would consist of referral to an immunology specialist for appropriate in vitro testing. The advantage of the latter method comes from the fact that it is highly quantitative and directly comparable with reference standards. Third, a total serum hemolytic complement assay can be ordered to exclude deficiency of any of the components of the classic complement pathway. This test is highly sensitive to sample handling, and true deficiency is likely only if the total serum hemolytic complement is zero or near zero. (38) Next, a potential diagnosis of CGD should be examined using a dihydrorhodamine-1,2,3 flow cytometry–based assay. Nitroblue tetrazolium reduction is no longer preferred due to its subjectivity and lack of sensitivity. Clinicians should be aware that individuals with myeloperoxidase and glucose-6-phosphate dehydrogenase deficiencies can have abnormal dihydrorhodamine-1,2,3 test results. Children whose clinical history may suggest cyclic neutropenia should be evaluated by serial complete blood cell counts with differential counts. This protocol involves obtaining counts 2 to 3 times weekly for 6 to 8 weeks. Finally, patients for whom ataxia-telangiectasia is suspected should be screened with a serum α-fetoprotein level, which is typically elevated in affected individuals.

Children with suspected PIDs should then be referred to a clinical immunology expert for further evaluation because many different subspecialized immune tests are available that help in the further delineation of the different PIDs. Such additional laboratory testing may be warranted, and genetic testing may be considered necessary in some individuals. (18) Importantly, we are rapidly moving toward a practice environment in which broad genetic testing (such as whole exome sequencing) may actually precede formal assessment of a PID in an otherwise sick child. This approach has the potential to conserve financial resources in some cases but often leaves the geneticist and immunologist with the task of determining whether certain genetic findings represent an explanation for the clinical and immunologic presentation. A detailed discourse concerning this topic exceeds the scope of this discussion, but the reader is referred to several excellent review articles. (39)(40)(41) Nonetheless, it is essential for the pediatrician to know that several different sequencing "panels" exist to allow for follow-up assessment of abnormal SCID newborn screening tests and can capture all known SCID-associated genes with rapid turnaround. Although genetic tests are truly empowering and can be definitive, they do not replace quantitative and functional immune tests, which are still needed to understand the severity of a given gene aberration.

Management of Children with PID

Infectious complications should be minimized as much as possible, and strategies should be dictated by the susceptibilities associated with the immunologic mechanism that is impaired. These precautions are especially important because any infection in an individual with PID has the potential to become severe, and repeated chest infections in particular can increase the risk of bronchiectasis and irreversible lung damage. Trimethoprim-sulfamethoxazole prophylaxis is indicated for the prevention of *Pneumocystis* pneumonia and is also used for prophylaxis against staphylococcal and nocardial infections in CGD. Children with susceptibility to atypical mycobacterial infections should be placed on azithromycin prophylaxis, and acyclovir is recommended as a prophylactic agent in individuals who are susceptible to invasive herpes simplex virus infections. Fluconazole can be used for prophylaxis against candidal infections, although some patients with chronic mucocutaneous candidiasis will require voriconazole for complete prevention. In children with CGD, itraconazole is typically used for prophylaxis against *Aspergillus* and other fungal infections. Antifungal prophylaxis is especially important in these patients, as *Aspergillus* infection represents the most significant cause of mortality. Children who are susceptible to *Cryptosporidium parvum* infections, such as boys with X-linked hyper-IgM syndrome, should avoid water parks and tap water. Live attenuated immunizations should not be given to individuals with certain PIDs and should, therefore, be approved by an immunology specialist before administration. (36) Live attenuated immunizations should be administered to family members and household contacts, however, to provide herd protection. (42) For all children, universal precautions, such as good handwashing, should be practiced. They do not need to be "kept in a bubble" but should be excluded from contact with individuals who have infections and from environments highly enriched for pathogens, such as child care. Children with severe T-cell deficiencies require reverse isolation in clinic and hospital settings. If transfusions become necessary for these individuals, they should receive only irradiated, cytomegalovirus-negative blood products. In all children with PIDs, a low index of suspicion should be entertained for infections. Antimicrobial drug therapy should be given promptly and withdrawn cautiously. It is also important to note that many of these practices become unnecessary in patients who have achieved full immune reconstitution through definitive curative measures, such as hematopoietic stem cell transplant or gene therapy.

Finally, more advanced treatment options should be pursued with input from an expert in PIDs. For example, IgG replacement is fully indicated as a therapy for PIDs that contain humoral deficiency as a component and should be used to treat such patients with PID accordingly. (43) Certainly, a wide array of IgG replacement options exists, and best practice continues to evolve. (44) Furthermore, as knowledge increases regarding the defective mechanisms responsible for impaired immunity for various PIDs, novel targeted biological therapies are being developed and tested to more specifically restore appropriate immune function in these individuals. (45)(46) Ultimately, the greatest opportunity for definitive treatment for most children with PIDs will come through continued improvements in hematopoietic stem cell transplant and increasing advances in gene therapy, as directed by an immunology specialist.

SECONDARY IMMUNODEFICIENCIES

Secondary causes of immunodeficiency should always be excluded in children with suspected PIDs. A brief review of these etiologies follows.

Iatrogenic causes of immunodeficiency must be considered. Medications stand as well-established causes of IgA deficiency and include antiepileptic drugs, such as phenytoin, carbamazepine, valproic acid, and zonisamide. (47) IgA deficiency has also been linked to use of nonsteroidal anti-inflammatory drugs. (47) Other medications associated with hypogammaglobulinemia include anti-inflammatory compounds (eg, sulfasalazine, gold, penicillamine, and hydroxychloroquine). (48) Many medications given for chemotherapy in the transplant setting or for treatment of malignancies, such as cyclosporine, tacrolimus, mycophenolate mofetil, cyclophosphamide, azathioprine, and 6-mercaptopurine, can cause hypogammaglobulinemia and secondary T-cell deficiencies. Corticosteroids also suppress T-cell function and impair wound healing, and they have been proposed to induce hypogammaglobulinemia if administered for extended periods. (48) Targeted biological modifiers are being implemented in a variety of disease conditions, such as autoimmune or inflammatory diseases and solid organ transplant, and they have been demonstrated to cause secondary immunodeficiency. (46)(49) The primary mechanism consists of intentional disruption of the immunologic host defense processes that are causing the undesirable clinical condition. For example, individuals who are receiving anti–tumor necrosis factor α therapy for inflammatory bowel disease are well-known to have increased risk for *Mycobacterium tuberculosis* infection or reactivation. Several newer biologic therapies (*eg*, rituximab and anti-CD19 chimeric antigen receptor T cells) are designed to cause depletion of B cells and result in hypogammaglobulinemia. Finally, surgical injury to the thoracic duct can cause hypogammaglobulinemia and quantitative T-cell deficiency through loss of lymphatic contents into the pleural cavity.

Other mechanisms of immunoglobulin and lymphocyte losses must be excluded as well. Additional explanations for pulmonary losses include chylothorax or exudative pleural effusions from obstruction of lymphatic flow or perturbed intrathoracic pressure. Gastrointestinal losses can also represent a significant cause of secondary immunodeficiency. Hypogammaglobulinemia, particularly loss of IgG, and lymphopenia can be observed in children with intestinal lymphangiectasia. Other sources of gastrointestinal losses include inflammatory bowel disease and chronic diarrhea. Last, nephrotic syndrome can even lead to IgG deficiency in some patients through urinary losses.

Nutritional status cannot be underestimated as a secondary cause of immunodeficiency, and it is said to represent the most common cause of an immune deficiency. (50)(51) Severe malnutrition results in decreased production of secretory IgA by mucosal tissues and lower numbers of B cells. Thymic involution occurs, total T and $CD4^+$ T-cell counts decrease, and T-cell proliferation to mitogens and antigens becomes diminished. The absence of specific nutrients can affect immunity in a variety of manners. For example, lack of protein results in overall leukopenia and diminished innate immune function. (52) Zinc deficiency, on the other hand, results in impaired neutrophil chemotaxis and phagocytosis, natural killer cell cytotoxicity, and T-cell differentiation. (53) Vitamin E deficiency has been reported to cause decreased T-cell function, and vitamin B_6 deficiency is associated with lymphopenia, decreased antibody production, and lower T-cell proliferative responses to mitogens. (54) Furthermore, vitamin C deficiency is known to result in susceptibility to infections, especially pneumonia, and poor wound healing through impaired neutrophil chemotaxis, phagocytosis, and killing activity. (55) On the opposite end of the spectrum, obesity can impair neutrophil activity, lymphocyte proliferation, and T-cell development. (56) Thus, nutritional factors must be assessed.

Physiologic and psychological stress can also cause secondary immunodeficiency. (57) For example, critically ill postinjury patients have been shown to have impaired neutrophil phagocytosis and killing of *S aureus*. (58) As a second example, brain injury induces interleukin-10–mediated suppression of immune function. (59) In addition, psychosocial stressors can certainly affect children, whether at home, at school, or in other settings. For instance, children with depression can have decreased neutrophil phagocytosis and bactericidal activity toward *S aureus*. (60) On the whole, few studies have examined the effect of psychological stressors on immune function in children, but lessons may be learned from stress in adults, which is associated with reduced secondary antibody responses and lymphocyte proliferative responses to mitogens among other immunologic changes. (61)(62)

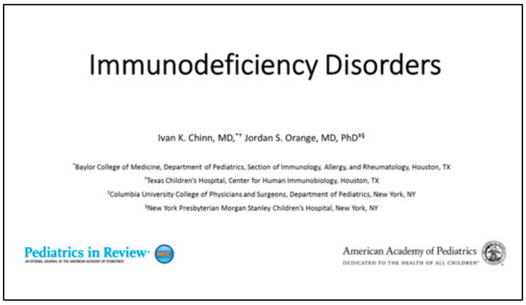
Human immunodeficiency virus (HIV) infection remains the most well-studied cause of secondary immunodeficiency; a comprehensive discussion remains beyond the scope of this review. HIV infection should be excluded by antibody- and antigen-based assays combined with nucleic acid testing. (63) For neonates, only virologic testing should be performed due to transmission of maternal antibodies. These nucleic acid–based tests should be performed at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months. (64)

Other factors should be investigated as potential secondary causes of immunodeficiency. Anatomical issues, such as eustachian tube dysfunction and congenital fistulas, can lead to recurrent infections. Atopy can produce adenoidal hypertrophy that results in recurrent otitis media or sinusitis. It can also contribute to asthma, which may be misdiagnosed as recurrent pneumonia or bronchitis. Furthermore, allergic sensitization can exacerbate eczema, which can predispose toward recurrent cutaneous infections. In terms of oncologic etiologies, multiple myeloma and chronic lymphocytic leukemia are known to produce secondary immunodeficiency, but these malignancies do not commonly occur in children. (65) No large studies have been conducted to examine the prevalence of secondary immunodeficiency in pediatric malignancies, however. Other disease conditions, such as cystic fibrosis and diabetes mellitus, (66) are known to favor the appearance of recurrent infections. SLE has been associated with IgA deficiency, but it remains uncertain whether the correlation is causal. (67)(68) Certainly, some effect on immune function is likely, as 1 of the 11 criteria used for diagnosis includes leukopenia or lymphopenia. Infections themselves can suppress immunity. A well-established example is provided by measles infection, which can produce profound impairment of B- and T-cell function. (69) Finally, preterm infants are born with an immunocompromised state. (70) Transfer of maternal antibodies begins during the second trimester but accelerates during the final trimester. Mature T cells can be detected at 15 to 16 weeks of gestation, but polyclonal repertoire diversity is not achieved until 22 to 26 weeks of gestation, and thymic output remains low, resulting in low T-cell receptor excision circle levels and abnormal newborn screening tests for SCID. (71)(72)

CONCLUSIONS

Clinicians must maintain a high index of suspicion for immunodeficiency disorders in pediatric patients. Decades of ongoing exploration and study affirm the notion that PIDs are neither rare nor necessarily intimidating to diagnose and manage. Instead, timely recognition of these conditions followed by appropriate testing and referral to an immunology specialist remains indispensable for realizing essential strategies to provide optimal health and well-being for these children. As such, early symptoms or cues present a critical window of opportunity during which a diagnosis can be established while still permitting transformative or even curative treatments to promote longevity and quality of life.

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/40/5/229.supplemental.**



Immunodeficiency Disorders

Ivan K. Chinn, MD,*† Jordan S. Orange, MD, PhD‡§

*Baylor College of Medicine, Department of Pediatrics, Section of Immunology, Allergy, and Rheumatology, Houston, TX
†Texas Children's Hospital, Center for Human Immunobiology, Houston, TX
‡Columbia University College of Physicians and Surgeons, Department of Pediatrics, New York, NY
§New York Presbyterian Morgan Stanley Children's Hospital, New York, NY

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Summary

- Based on growing research evidence as well as consensus, primary immunodeficiencies (PIDs) are not rare conditions. More than 300 different PIDs exist, and the prevalence of PID is approximately 1 in every 1,200 to 2,000 individuals. (1)(2)(3) Because most PIDs have well-defined genetic etiologies, in the evaluation for PID, clinicians should solicit information about consanguinity or about family members with immune deficiency, recurrent or severe infections, or early mortality.
- Based on strong research evidence as well as consensus, severe combined immunodeficiency disease (SCID) is a pediatric emergency due to profound absence of humoral and cellular immunity secondary to lack of T cells. (6)(7) The condition may be recognized by abnormal newborn screening test results, an absolute lymphocyte count less than 2,500/μL (2.5×10^9/L) in a term neonate, opportunistic infections, absence of cardiothymic silhouette in an infant, failure to thrive, and paucity of lymphatic tissues. In fact, all pediatric patients who have unexplained failure to thrive and lack of lymphoid tissue should be assessed for PID. Any concern for SCID warrants prompt evaluation by an immunology specialist.
- Based on consensus as well as some research evidence, receipt of an abnormal newborn screening test result for SCID should compel the pediatrician to obtain immediate consultation with an immunology specialist. A complete blood cell count with a manual differential count should be obtained expeditiously to assess for absolute lymphopenia. (36)
- Based on collective research evidence as well as consensus, although healthy children may have more than 3 episodes of otitis media and up to 11 upper respiratory tract infections each year, (31)(32) children with uncharacteristically recurrent, severe, or unusual infections should be tested for PIDs. Children with recurrent sinopulmonary tract infections, especially after 3 to 4 months of age, should be evaluated for humoral immune deficiencies and other PIDs. (5) Children with invasive infections and poor wound healing should be tested for defects in phagocytic number or function. Chronic granulomatous disease should be suspected in a child with infection due to an unusual bacterial or fungal organism. (8)(10) Natural killer cell deficiency should be considered in a child with recurrent, severe, or unusual herpesviral infections. (11)(12) Children with atypical mycobacterial infections and chronic mucocutaneous candidiasis should be assessed for PIDs. (13)(14) Children with susceptibility to neisserial pathogens should be evaluated for primary complement deficiencies. (17)
- Based primarily on consensus due to lack of large clinical studies, children with PIDs can present with noninfectious issues. Children with early- or very early–onset enteropathy or inflammatory bowel disease should be evaluated for underlying PIDs. (19) PIDs should be considered in children with severe eczema, neutrophilic pustular dermatosis, ectodermal dysplasia, cutaneous granulomas, abnormal skin or hair pigmentation, and cold-induced urticaria. (20)(21) PIDs can be associated with early-onset autoimmune disease. (22)(23)(24)(25)(26) Children with early-onset endocrinopathies should be evaluated for underlying PIDs. PIDs can also present in children as lymphoproliferative disease and hemophagocytic lymphohistiocytosis. (28) Several neurologic signs, including ataxia, hearing loss, and developmental delay, are associated with PIDs. (29)(30) Children with PIDs are known to present with interstitial lung disease, pulmonary alveolar proteinosis, pulmonary capillaritis, or eosinophilic pneumonia. Allergies and skeletal dysplasia can be associated with PIDs.
- Based on consensus as well as established research evidence, although children with suspected PID should be referred to an immunology specialist for assistance with diagnostic evaluation, test results interpretation, and management recommendations, there are widely available testing methods for evaluating for PIDs before referral. Because most PIDs affect humoral immunity, children with suspected PIDs should be screened by measurement of serum immunoglobulin levels and specific antibody responses to immunizations. (3)(34)(35) Additional tests that should be considered include an absolute lymphocyte count to evaluate for quantitative T-cell deficiency, delayed-type hypersensitivity skin testing to examine T-cell function, a total serum hemolytic complement assay to investigate for primary complement pathway deficiencies, and a dihydrorhodamine-1,2,3 assay to assess for chronic granulomatous disease.
- Based on consensus as well as some research evidence, in children with PIDs, infections should be minimized using appropriate antimicrobial prophylaxes, social and environmental preventive measures, and other universal precautions.
- Based on strong research evidence as well as consensus, IgG replacement stands as an effective and potentially lifesaving treatment for children with severe or functional humoral immune deficiency. (42)(43)
- Based on some research evidence as well as consensus, secondary causes of immunodeficiency must be excluded in children with suspected PIDs. Various medications, especially antiepileptic, anti-inflammatory, chemotherapeutic, and immune modulatory compounds, are known to cause secondary immunodeficiencies. (45)(46)(47)(48) Physiologic losses of immunoglobulins and lymphocytes can result in secondary immunodeficiency. Nutritional deficits and excess can produce secondary immunodeficiency, as can physiologic and psychosocial stress. (49)(50)(51)(52)(53)(54)(55)(56)(57)(58)(59)(60)(61) Human immunodeficiency virus infection must be excluded in children with suspected immunodeficiency. (62)(63) Other common secondary causes of immunodeficiency that must be considered include anatomical mechanisms, atopy, other underlying disease conditions, infection-induced immune suppression, and prematurity. (64)(65)(66)(67)(68)(69)(70)(71)

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1. A 5-year-old girl, new to your practice, is brought to the clinic by her parents with concerns for attention-deficit/hyperactivity disorder and autism because of her cognitive and behavioral problems. Her medical history is significant for tetralogy of Fallot, which was repaired at 5 months of age, frequent upper respiratory tract infections, and recurrent tinea capitis. Which of the following is the most likely diagnosis to consider in this patient?
   - A. Aicardi-Goutières syndrome.
   - B. Chédiak-Higashi syndrome.
   - C. Chronic granulomatous disease.
   - D. DiGeorge syndrome.
   - E. Wiskott-Aldrich syndrome.
2. A 6-year-old girl in your practice has a history of severe eczema, recurrent staphylococcal abscesses, mild facial dysmorphism, and scoliosis. Her older sister has similar symptoms and her mother has a history of recurrent skin and lung abscesses. Which of the following laboratory tests is the most appropriate initial test that is likely to be useful in making a diagnosis in this patient?
   - A. Total serum hemolytic complement level.
   - B. Dihydrorhodamine-1,2,3 flow cytometry.
   - C. Platelet count.
   - D. Quantitative immunoglobulins.
   - E. T-cell flow cytometry.
3. A 1-month-old infant, followed in your practice, is found to have an absent thymic shadow when a chest radiograph was obtained during an episode of bronchiolitis. A complete blood cell count demonstrates marked lymphopenia. Which of the following is the most appropriate next step in the care of this infant?
   - A. Initiate antibiotic prophylaxis with azithromycin.
   - B. Measure quantitative immunoglobulins.
   - C. Obtain a complete blood cell count with a manual differential count twice weekly for 6 to 8 weeks.
   - D. Refer to an immunology specialist.
   - E. Test for human immunodeficiency virus infection using a nucleic acid–based test.
4. A 30-month-old boy was hospitalized for operative drainage of bilateral cervical adenitis due to *Staphylococcus aureus* infection. His medical history includes a previous hospitalization for pneumonia with blood culture positive for *Klebsiella pneumoniae*, as well as recurrent fevers and pyoderma. Dihydrorhodamine-1,2,3 assay results are abnormal. Which of the following is the most likely diagnosis in this patient?
   - A. Ataxia-telangiectasia.
   - B. Chronic granulomatous disease.
   - C. Common variable immunodeficiency.
   - D. Cyclic neutropenia.
   - E. Leukocyte adhesion deficiency.
5. Newborn screening results for an infant in your practice have just returned positive for severe combined immunodeficiency (SCID). Which of the following is the most appropriate next step in the management of this patient?
   - A. Measure quantitative immunoglobulin levels.
   - B. Order a gene sequencing panel for SCID.
   - C. Reassure the parents that this is likely a false-positive result.
   - D. Repeat the newborn screen.
   - E. Seek immediate specialty consultation.

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Immunodeficiency Disorders

Ivan K. Chinn and Jordan S. Orange

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Index of Suspicion

1 Cardiac Arrest in a 2-month-old Boy with a Prenatal Course Complicated by Alloimmunization

Millie R. Chang, MD,* Andrew H. Chon, MD,† Jacquelyn Baskin, MD,‡§
Ali Nael, MD,*¶ Ramen H. Chmait, MD†

*Department of Pediatrics, §Children's Center for Cancer and Blood Disease, ¶Department of Pathology, Children's Hospital Los Angeles, Los Angeles, CA
†Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, ‡Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA

EDITOR'S NOTE

Children face a daily balancing act between antigens, allergy, and immunity. Sometimes, that balance turns pathologic. Either the antigen can "win" or the immune response can end up hurting the host. In the review articles and case reports this month, we are reminded of immune reactions gone awry, and we learn how to care for affected children.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A 30-year-old gravida 2, para 1 woman with an intrauterine pregnancy at 29 1/7 weeks' gestation was referred for suspected fetal anemia secondary to rhesus (D) (Rh[D]) alloimmunization. The fetus received 3 intrauterine transfusions (IUTs) during the pregnancy (Table). The patient delivered vaginally at 37 1/7 weeks' gestation. The birthweight was 2,680 g, and Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. On postnatal day 1, phototherapy was initiated for hyperbilirubinemia. On postnatal day 2, a complete blood cell count showed a white blood cell count of 2,500/μL (2.5×10^9/L), a hemoglobin (Hb) level of 16.7 g/dL (167 g/L), a hematocrit level of 46.6%, and a platelet count of $68 \times 10^3/\mu$L (68×10^9/L). The baby was discharged on postnatal day 3 when phototherapy was discontinued. Repeated bilirubin levels were within normal limits at an outpatient follow-up visit on postnatal day 4. The baby was seen in the clinic on postnatal day 10 for a health supervision visit, and a follow-up appointment was scheduled for 2 months of age.

On postnatal day 49, the parents noted the baby to be jaundiced, and they contacted the primary pediatrician, who instructed them to bring the child to the clinic later that week. However, on postnatal day 51, the baby was found to be apneic and cyanotic at home. On arrival by the paramedics, the baby was in pulseless electrical activity. Cardiopulmonary resuscitation (CPR) was initiated en

AUTHOR DISCLOSURE Drs Chang, Chon, Baskin, Nael, and Chmait have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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TABLE. **Intrauterine Transfusions Performed During Pregnancy for the Treatment of Rhesus (D) Alloimmunization**

TRANSFUSION NO.	GESTATIONAL AGE, WK	HEMOGLOBIN, G/DL (G/L)	
		PRETRANSFUSION	POSTTRANSFUSION
1	29 2/7	6.9 (69)	14.2 (142)
2	31 2/7	8.4 (84)	15.1 (151)
3	34 2/7	8.7 (87)	15.9 (159)

route to the hospital, and spontaneous circulation returned after 60 minutes of CPR.

DISCUSSION

Hospital admission laboratory test results were consistent with severe metabolic acidosis (pH <6.5, bicarbonate <5 mEq/L [<5 mmol/L]) and pancytopenia (white blood cell count 1,100/μL [1.1×10^9/L], Hb 1.5 g/dL [15 g/L], hematocrit 6.1%, platelet count $7 \times 10^3/\mu$L [7×10^9/L]). The patient was transfused 10 mL/kg of packed red blood cells (pRBCs) and was transferred to a PICU. On arrival at the PICU, the boy deteriorated again, requiring an additional 30 minutes of CPR, at which point his parents elected to discontinue resuscitative efforts given the grave prognosis.

Autopsy was performed. Microscopic examination of the bone marrow revealed normocellular marrow with trilineage hematopoiesis and approximately 90% cellularity (Fig, A and B). There was a relative erythroid hyperplasia (myeloid-to-erythroid ratio was estimated to be 1:3-4), which was consistent with a bone marrow response to ongoing hemolysis. Most erythroid precursor cells had arrest at the late normoblast maturation stage. The myeloid precursors showed extensive left-shifted maturation, with essentially no mature neutrophils visible. Adequate megakaryocytes were identified, with occasional immature forms. Additional findings were steatosis and panlobular iron deposition (3+) in the liver (Fig, C) consistent with a history of intrauterine transfusion, and extramedullary hematopoiesis and white pulp depletion in the spleen (Fig, D), suggestive of inadequate bone marrow erythropoiesis.

The Condition

Anemia in a 2-month-old infant can be due to hemolysis that is immune mediated or hereditary, blood loss, Hb abnormalities, exposure to toxins, infections, or, rarely, iron deficiency. We describe a case of immune-mediated hemolytic disease of the fetus and newborn (HDFN) due to Rh(D) alloimmunization that was successfully treated in utero with serial transfusions, resulting in an uncomplicated birth but, unfortunately, ending with the baby's demise at 2 months of age secondary to complications of subsequent untreated severe anemia. The pathophysiology of HDFN results from a Rh(D)-negative mother being sensitized to Rh(D)-positive fetal RBCs and subsequently having transplacental passage of maternal anti-D immunoglobulin G (IgG) antibodies into the fetal circulation. The IgG antibodies then cause fetal and neonatal anemia from both destruction of RBCs and bone marrow suppression of erythropoiesis.

Once a common condition, HDFN dramatically reduced in incidence after the implementation of Rh(D) immunoprophylaxis, with an associated reduction in mortality from 46 per 100,000 births to 1.6 per 100,000 births. (1)(2) However, the success of prevention has resulted in current physicians having limited experience caring for these patients. This is compounded by the fact that newborns treated in utero appear healthy at birth, which may lead to a false sense of reassurance for both parents and physicians.

Management

Prenatal management of alloimmunization has been described extensively. (3) Maternal laboratory testing and serial fetal Doppler velocimetry of the middle cerebral artery peak systolic velocity can accurately identify the at-risk fetus. (4) The primary method to definitively diagnose fetal anemia is ultrasonography-guided sampling of the fetal blood. (5) Once anemia is confirmed, an IUT can be performed. (4)(5) IUTs are generally conducted at specialized fetal therapy centers. The procedure-related fetal loss rate is approximately 1%. (5)

The goals of immediate postnatal management in neonates with HDFN are focused on the identification and treatment of anemia and hyperbilirubinemia. Persistent or worsening postnatal anemia can be caused by several mechanisms of variable timing, so close postnatal surveillance for the first few months after birth is warranted. (6)(7)(8) Immediately after birth, the Hb level may be normal

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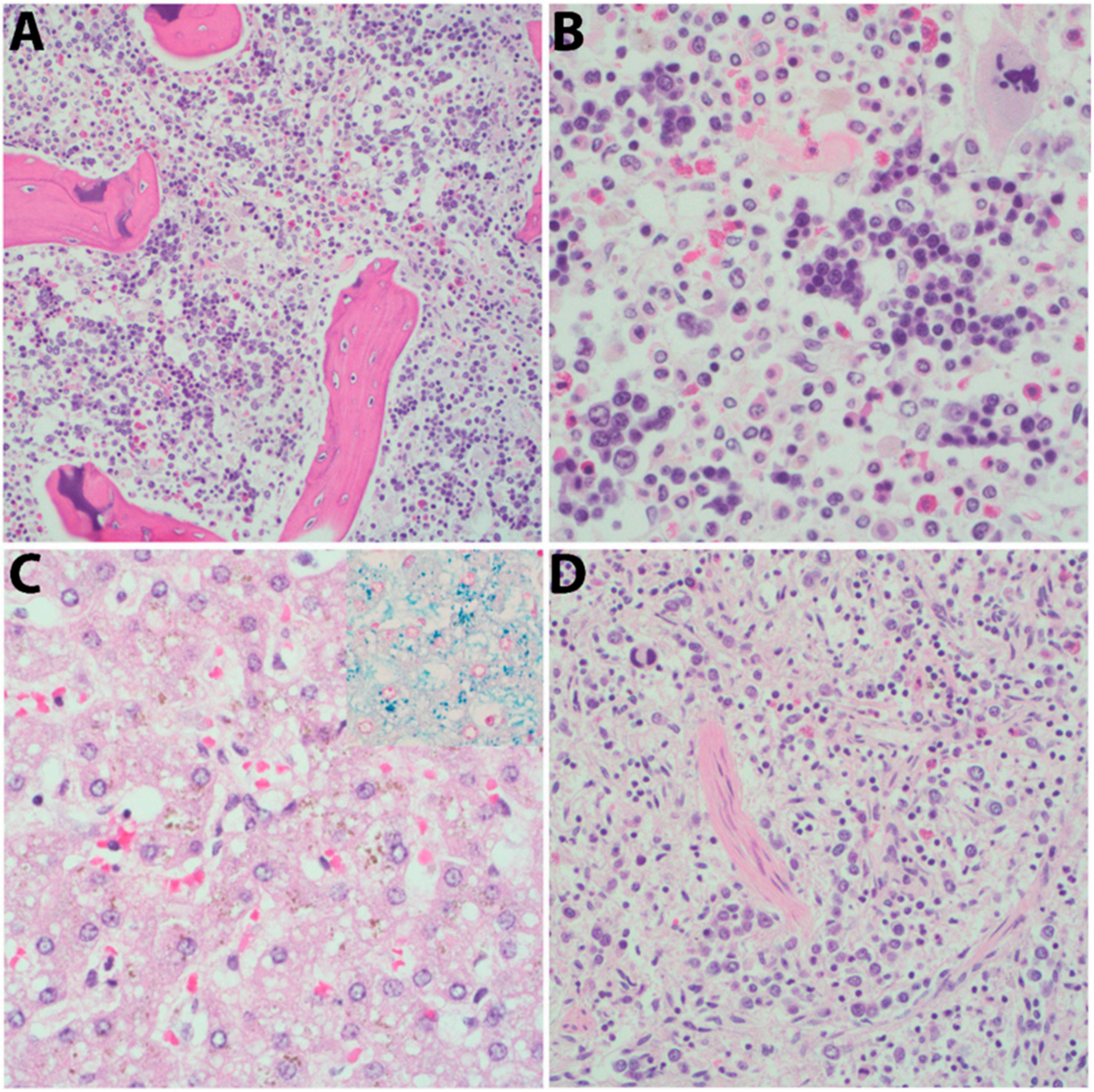

Figure. A and B. Microscopic examination of the bone marrow reveals normocellular bone marrow with trilineage hematopoiesis. There is a relative erythroid hyperplasia with predominance of normoblasts at different stages and decreased myeloid cells with left-shifted maturation (hematoxylin-eosin [H&E], original magnification ×100 and ×200, respectively). C. Section from liver shows macrovesicular and microvesicular steatosis with frequent intracellular and Kupffer cell hemosiderosis. Inset: Iron special stain. D. Section of spleen reveals extramedullary hematopoiesis and white pulp depletion (C and D: H&E, original magnification ×200).

or mildly decreased, which may give the parents and the pediatrician a false sense of reassurance. However, in the coming days to weeks, the Hb level may drop significantly due to persistent maternal IgG circulating in the baby and destroying newly produced endogenous Rh(D)-positive RBCs. Maternal IgG antibodies causing hemolysis can persist for up to several months. An additional mechanism is hyporegenerative anemia, which may begin in utero and can persist for up to several weeks after delivery. (6)(9)(10) The etiology of hyporegenerative anemia is unclear; however, immune destruction of RBC precursors, (11)(12) bone marrow suppression from IUT itself, (12) and erythropoietin deficiency (7)(8)(9)(13)(14) are implicated. Bone marrow suppression by IUTs remains controversial because bone marrow suppression has also been described even before the implementation of IUTs. (6)(7)(15) Some studies have shown that the rate of postnatal transfusions is increased in neonates who have received IUTs (77%–89%)

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compared with neonates not treated with IUTs (27%–67%), (6)(7)(16) particularly during their first 6 months after birth. (7),(10)(17) Furthermore, there can be additional bone marrow suppression in the event of postnatal transfusions, which can be further compounded as the infant reaches his or her physiologic nadir at 6 to 12 weeks after birth. (6)(18)(19)

Considering that severe anemia can occur either early (≤1 week) or late (>1 week to 6 months) after delivery, (6)(7)(8)(20) serial Hb monitoring after hospital discharge is crucial. The primary management of postnatal anemia is via transfusions of pRBCs. Up to 40% of infants require a pRBC transfusion for early-onset anemia and up to 80% will require at least 1 pRBC transfusion for late-onset anemia. (6)(7)(8)(20)(21) Other supplementary strategies to treat postnatal anemia include administration of erythropoietin, (22)(23) folic acid, (24)(25) and intravenous immunoglobulin. (8)(26)(27) Also, parents and pediatricians should be aware of and monitor for signs and symptoms of severe anemia, such as fatigue, difficulty with feeding, irritability, tachycardia, or paleness.

Hyperbilirubinemia occurs secondary to RBC breakdown due to circulating antibodies and should be promptly addressed to prevent progression to kernicterus. It is most commonly managed with phototherapy or exchange transfusion. (8)(16) Phototherapy increases the excretion of bilirubin products in the urine. An exchange transfusion filters the bilirubin and remaining maternal antibodies from the infant's peripheral blood and reduces the degree of hemolysis by providing immunologically compatible donor blood. (28)

In this case, the newborn status was optimized by serial fetal IUTs, which led to a false sense of reassurance of the baby's status. Thus, subsequent development of anemia was not detected, causing the baby's demise at 2 months of age secondary to complications of untreated severe anemia. We recommend close follow-up with serial Hb levels for at least the first 3 months after birth or until the physiologic nadir occurs. (6)(18)(19)

Lessons for the Clinician

- Although the postnatal management of hemolytic disease of the fetus and newborn (HDFN) is not uniform, it is important for pediatricians to be educated on this matter because the resulting anemia and hyperbilirubinemia are both treatable morbidities.
- Strict postnatal surveillance for anemia is critical in HDFN-affected babies, including those who appear healthy, with normal hemoglobin levels immediately after delivery.
- Serial assessments for the development of anemia should be performed for at least the first 3 months after birth or until resolution of the physiologic nadir occurs. (6)(18)(19)
- The detection of jaundice in an infant with a known history of alloimmunization requires urgent medical evaluation, including a complete blood cell count and serum bilirubin concentration.
- The pediatrician should work in conjunction with a hematologist to ensure a safe postnatal course and follow-up to optimize outcomes for this treatable disease.

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Case 1: Cardiac Arrest in a 2-month-old Boy with a Prenatal Course Complicated by Alloimmunization

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Case 1: Cardiac Arrest in a 2-month-old Boy with a Prenatal Course Complicated by Alloimmunization

Millie R. Chang, Andrew H. Chon, Jacquelyn Baskin, Ali Nael and Ramen H. Chmait
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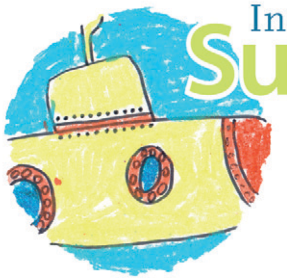

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2 Acute Onset and Worsening of Anemia in a 3-year-old Boy

Sofia Khera, MD,*[†] Zoabe Hafeez, MD,*[†] Amanda Padilla, MD[†‡]

*Pediatric Hospital Medicine and [‡]Department of Pediatrics, McGovern Medical School,
University of Texas Health Science Center at Houston, Houston, TX
[†]Children's Memorial Hermann Hospital, Houston, TX

PRESENTATION

A 3-year-old boy of Persian descent presents to his primary care physician with 2 days of fever to a temperature of 101.8°F (38.8°C) and a 1-day history of jaundice. A review of systems reveals that he has decreased oral intake, headache, looser stools that are orange in color, and 3 recent episodes of nonbloody, nonbilious vomiting. At the visit he has bright red urination. The patient has a brother who was treated for streptococcal pharyngitis 1.5 weeks ago. His medical history is not significant for any previous illnesses. His birth history reveals that the patient was jaundiced but did not require any phototherapy. His family history does not reveal any kidney or hematologic abnormalities except for a brother who required phototherapy at birth.

Results of abdominal ultrasonography and chest radiography are normal. The patient is admitted to the hospital with a heart rate of 98 beats/min, a blood pressure of 108/73 mm Hg, a respiratory rate of 22 breaths/min, and a temperature of 97.5°F (36.4°C). On physical examination the patient appears tired and is noted to have jaundice with mild scleral icterus. His oropharynx is clear, with mildly erythematous tonsils but no exudates, and he has serous fluid behind the right tympanic membrane. The patient has no rash, no palpable hepatosplenomegaly, and no cervical, axillary, or inguinal lymphadenopathy.

Initial laboratory tests show urine analysis with brown color, a glucose level of 250 mg/dL (13.9 mmol/L), large blood cells, ketone levels of 40 mg/dL, a protein level greater than 0.3 g/dL (>3 g/L), a urobilinogen level greater than 8.0 mg/dL (0.44 mmol/L), a moderate bilirubin level, moderate leukocyte esterase, positive nitrite, 0.2 white blood cells per high-power field, 6 to 10 red blood cells per high-power field, moderate bacteria, occasional squamous epithelial cells, and many amorphous crystals. The serum electrolytes and creatinine level are within normal limits. The alanine aminotransferase level is 27 U/L (0.45 μkat/L), aspartate aminotransferase level is 178 U/L (2.97 μkat/L), alkaline phosphatase level is 245 U/L (4.09 μkat/L), and total bilirubin level is 4.9 mg/dL (83.8 μmol/L).

A complete blood cell (CBC) count shows a white blood cell count of 14,400/μL (14.4 × 10^9/L), a hemoglobin level of 8.3 g/dL (83 g/L), a hematocrit value of 23.4%, and a normal concentration of platelets. His mean corpuscular volume is 74 fL, which is the lower end of normal for his age. His red blood cell

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distribution width is 14.4 fL, which is the upper limit of normal for his age. He has normal mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. Other tests included a rapid mononucleosis assay, a hepatitis B surface antigen, and a hepatitis C antibody, which are negative, and an antistreptolysin O titer, which is normal. The γ-glutamyltransferase level is less than 3 U/L ($<$0.05 μkat/L), and coagulation studies show a prothrombin time of 14.7 seconds, an international normalized ratio of 1.13, and a partial thromboplastin time of 28.6 seconds. Rapid influenza nasopharyngeal and streptococcal throat swabs are both negative.

The patient has 2 voids with black-colored urine 4 hours after admission. A repeated CBC count shows that the hemoglobin level has decreased to 6.0 g/dL (60 g/L) and the hematocrit level has decreased to 16.9%. Additional laboratory tests show a lactate dehydrogenase level of 2,936 U/L (49.0 μkat/L), a significantly decreased haptoglobin level of less than 8 mg/dL ($<$80 mg/L), and a total bilirubin level of 3.3 mg/dL (56.4 μmol/L), with a 0.3 mg/dL (5.1 μmol/L) direct component. The reticulocyte count is mildly elevated at 1.8%, the C3 level is slightly decreased at 84 mg/dL, and the immunoglobulin (Ig) A level is 95 mg/dL (950 mg/L). Further testing reveals the diagnosis for this patient.

DISCUSSION

Hemolytic anemias are diagnosed in anemic patients who have an elevated reticulocyte count, indicating an appropriate bone marrow response. These patients commonly have elevated intracellular markers, such as bilirubin and lactate dehydrogenase, and decreased haptoglobin levels. Hemolytic anemia has multiple causes and variable presentations.

Hemolytic anemias can be either cellular or extracellular. Cellular diagnoses are due to pathology with the red blood cell membrane, enzymes, or hemoglobin. Extracellular diagnoses indicate a pathology that destroys the red blood cell externally, such as antibodies, mechanical factors, or plasma factors. Most cellular defects are inherited, and most extracellular defects are acquired. (1)

This patient is unlikely to have a cellular defect, especially because he has not had any previous episodes of hemolysis, his normal newborn screen rules out sickle cell disease, and his family history is negative for inherited cellular defects. Most red blood cell membrane defects would result in abnormally shaped red blood cells on a peripheral smear, such as spherocytes or elliptocytes, which can also result in splenomegaly. None of these were identified in our patient.

Etiologies for extracellular defects include autoimmune disorders or fragmentation due to direct damage to the red blood cell membrane. In addition, plasma factors, such as liver disease, abetalipoproteinemia, vitamin E deficiency, and Wilson disease, may cause extracellular hemolytic anemia. These plasma factors make red blood cells more susceptible to oxidative damage. Fragmentation can also occur due to infections that would lead to disseminated intravascular coagulationor hemolytic uremic syndrome. (1) The patient has a slightly elevated aspartate aminotransferase level but no other liver enzyme elevation that would indicate liver disease or concern for Wilson disease. The physical examination findings also did not reveal Kayser-Fleischer rings or any growth, vision, or balance problems, making abetalipoproteinemia or vitamin E deficiency less likely.

Furthermore, hemolytic anemias can also be classified by extravascular or intravascular hemolysis (Fig). In intravascular hemolysis, the red blood cell is damaged while in circulation, releasing hemoglobin. Examples of intravascular hemolysis are mechanical trauma (which can occur from prosthetic valves), complement fixation, or other toxic damage to the red blood cell. Free hemoglobin binds to circulating haptoglobin and is degraded and cleared by the liver. When haptoglobin becomes saturated by hemoglobin, unbound free hemoglobin is then excreted by the kidneys.

In contrast, extravascular hemolysis occurs when macrophages in the liver or the spleen engulf the red blood cell due to abnormalities with the red blood cell itself. Patients with exclusive extravascular hemolysis likely do not have red urine because all the hemoglobin then circulates through the liver. Our patient's presentation is most consistent with intravascular hemolysis due to the presence of hematuria and the lack of hepatosplenomegaly.

The Condition

Autoimmune hemolytic anemia (AHA) can occur intravascularly or extravascularly. Autoimmune etiology is determined by the direct antiglobulin test (DAT) or the Coombs test. The Coombs test result returned positive for our patient. The DAT IgG result returned negative but the DAT C3 result returned positive, which helps guide future therapy. The DAT can detect either IgG, indicating warm AHA, or fragments of complement, mainly C3, indicating cold agglutinin syndrome. Approximately 80% of AHAs are diagnosed as the warm antibody type. In cold antibody agglutinin syndrome, only complement is detected due to

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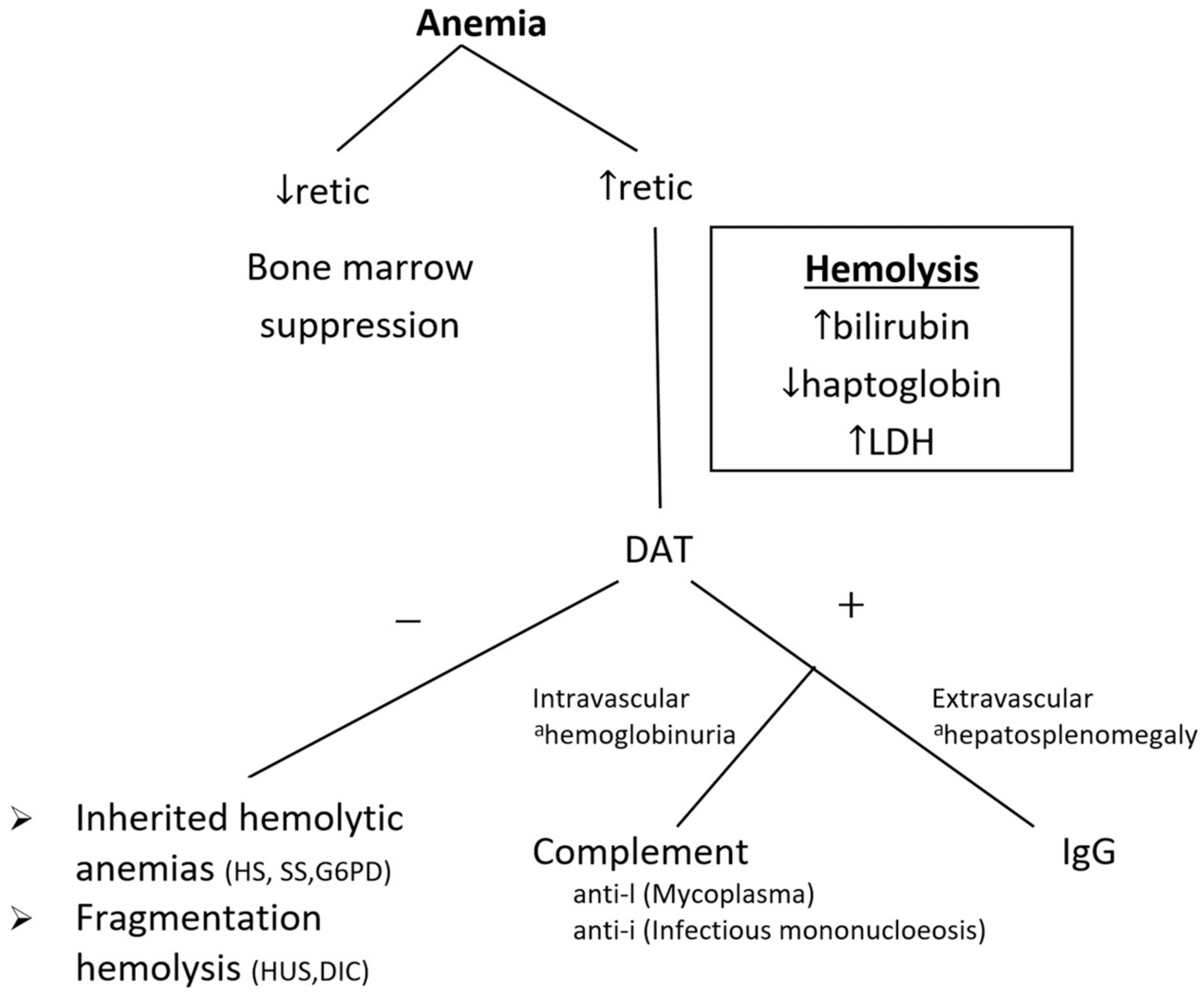

Figure. A basic approach to different hemolytic anemia diagnoses. DIC=disseminated intravascular coagulation, G6PD=glucose-6-phosphate dehydrogenase deficiency, HS=hereditary spherocytosis, HUS=hemolytic uremic syndrome, IgG=immunoglobulin G, LDH=lactate dehydrogenase, retic=reticulocyte count, SS=sickle cell anemia. [a] Commonly associated objective findings.

dissociation of antibody during washing of red blood cells. Complement fixation occurs intravascularly, causing hemoglobinuria or red-colored urine. Hemoglobinuria is most often seen in cold agglutinin syndrome but also can be seen with some drug-induced immune hemolytic anemias, often caused by cephalosporins. (2)

Cold agglutinin syndrome can further be classified by the type of antigen that is involved: I or i. Anti-I is mostly seen in patients who have an infection with antibody-positive *Mycoplasma pneumoniae,* and anti-i is mostly seen in patients with acute infectious mononucleosis or Epstein-Barr virus infections. Both types can also be seen in patients with lymphomas. (2)

Management

If the patient has symptomatic anemia, a blood transfusion should be given. High-dose corticosteroids of 1 to 1.5 mg/kg may be started orally or intravenously depending on the patient's clinical status. Corticosteroids are continued at higher doses until the hematocrit level stabilizes. Then, corticosteroid therapy is weaned as the hemoglobin concentration continues to remain stable or increase. Corticosteroids are not discontinued until the DAT result becomes negative. Patients may require up to 6 months of therapy until stable remission is achieved. Splenectomy may be effective in patients with extravascular hemolysis or warm antibody–type hemolytic anemia. Rituximab is sometimes used for cold agglutinin syndrome AHA. Addressing the underlying disease process, such as infections or lymphomas, will help treat the cold agglutinin AHA as well. It is also important to maintain a normal body temperature because the hemolysis occurs if body temperatures drop below 98.6° F (37°C). (2)

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Follow-up

Our patient was diagnosed as having complement-positive AHA or cold agglutinin syndrome with no identified infectious agent or malignant association. His Epstein-Barr virus and *Mycoplasma* serologic tests did not reveal an acute infection. He received high-dose corticosteroids immediately once his DAT result returned positive. He also received a blood transfusion when his hemoglobin level dropped below 5 mg/dL (50 g/L). Intravenous corticosteroids were continued until the hemoglobin level stabilized and he was no longer having hemoglobinuria. He was then followed by a hematologist with weekly laboratory tests, and once his DAT result became negative he was weaned off of corticosteroids over a 2-month period. He was also diagnosed as having iron deficiency anemia because further history revealed excessive cow's milk intake, and his laboratory tests showed a mean corpuscular volume at the lower limit of normal and a red blood cell distribution width at the upper limit of normal. After he was given an iron infusion, his reticulocyte count significantly increased and eventually normalized during corticosteroid therapy. It was concluded that his initial reticulocyte count, although slightly elevated, was abnormally low for an anemic patient due to confounding iron deficiency anemia.

Lessons for the Clinician

- Hemolytic anemia is associated with an elevated reticulocyte count, elevated bilirubin level, elevated lactate dehydrogenase level, and decreased haptoglobin level.
- Consider hemolytic anemia as a diagnosis for patients with red or black urine due to hemoglobinuria.
- Hemoglobinuria is seen in intravascular hemolysis, which is present in complement-mediated autoimmune hemolytic anemia, also referred to as cold agglutinin syndrome.
- Direct antiglobulin or Coombs testing can help determine whether and which type of autoimmune hemolytic anemia is present.

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Case 2: Acute Onset and Worsening of Anemia in a 3-year-old Boy

Sofia Khera, Zoabe Hafeez and Amanda Padilla

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Sofia Khera, Zoabe Hafeez and Amanda Padilla

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3 Pain and Weakness in a 12-year-old Boy

Hillary Seidenberg, MD,* Deepa Kulkarni, MD*

Department of Pediatrics, UCLA Mattel Children's Hospital, Los Angeles, CA

PRESENTATION

A 12-year-old previously healthy boy presents to his pediatrician with right-sided posterior rib pain in the context of a recent respiratory infection without associated fever. Over the next 10 days he presents another 3 times with vague symptoms of left posterior neck pain, diffuse abdominal pain, nausea, and decreased oral intake. Results of abdominal imaging, a complete blood cell count, and a comprehensive metabolic panel are normal except for increased stool burden on radiography.

The following day he presents to the emergency department, where he complains of continued abdominal pain, decreased appetite, and no urine output for 24 hours. He receives intravenous fluids and analgesics, after which his urine output, energy, and general appearance improve, and he is deemed stable for discharge. As he is leaving the emergency department, he states that he is unable to walk and is having left arm weakness and multiple episodes of urinary incontinence. Physical examination is repeated, with vital signs significant for tachycardia (heart rate of 146 beats/min) and hypertension (blood pressure of 151/83 mm Hg). He has paralysis and hypertonia of his left upper and bilateral lower extremities, decreased deep tendon reflexes throughout all extremities, pain with movement of the body, palpable stool burden, and suprapubic fullness. His sensory examination findings are normal, with no specific sensory level.

He is admitted to the hospital for further evaluation. Results of serum studies are normal. Cerebrospinal fluid (CSF) studies show an elevated white blood cell count (112/μL [0.1 × 10^9/L]) but otherwise normal findings, including levels of protein (45 mg/dL [0.45 g/L]), glucose (58 mg/dL [3.2 mmol/L]), and red blood cells (2/μL [0.000002 × 10^{12}/L]). Neuroimaging is also performed. Magnetic resonance images (MRIs) of the brain are normal. MRI of the spine (Fig) reveals the diagnosis.

DISCUSSION

The patient was diagnosed as having acute transverse myelitis (ATM), specifically, longitudinally extensive transverse myelitis (LETM), defined as a spinal cord lesion affecting 3 or more vertebral segments.

The Condition

ATM is an inflammatory spinal cord syndrome characterized by motor, sensory, and autonomic deficits. The incidence is rare, estimated to be 2 per million children per year. (1) The age distribution of pediatric patients with ATM is

AUTHOR DISCLOSURE Drs Seidenberg and Kulkarni have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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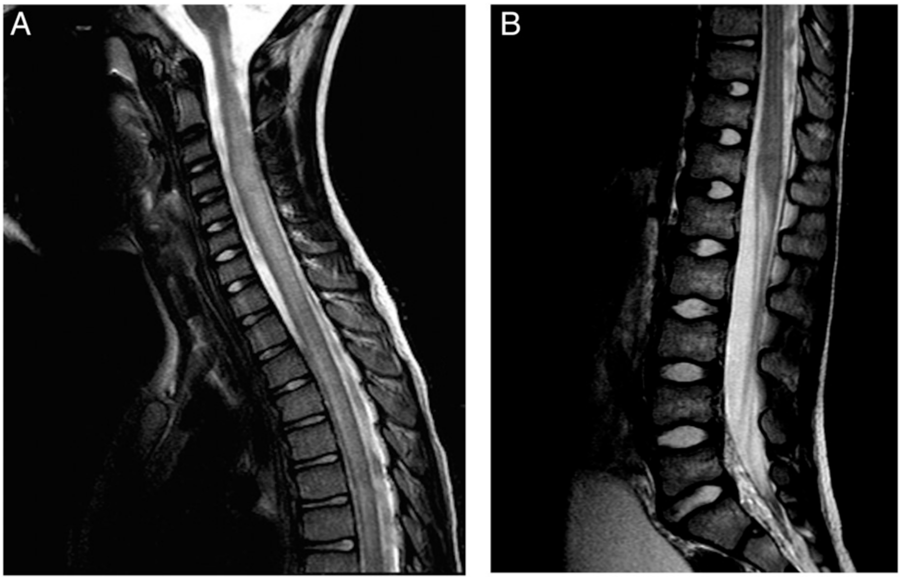

Figure. Magnetic resonance images of the spine show a hyperintense T2-weighted signal in the spinal cord from the cervicomedullary junction to the conus medullaris (20 vertebral segments). The signal abnormality involves gray and white matter of the central and posterior portions of the cord. A. Cervicomedullary junction to the eighth thoracic vertebra. B. Ninth thoracic vertebra to the conus medullaris, which ends at the first lumbar vertebra.

bimodal, with clusters at 0 to 2 and 5 to 17 years of age. (2)(3) Patients often have a preceding febrile illness. Symptoms are usually bilateral and may progress to nadir in as quickly as 4 hours or as long as 21 days. (4)

The patient discussed previously herein had an initially subtle presentation with pain, which is the presenting symptom in most children. He did have a preceding illness, but he was afebrile. His increased stool burden may have been representative of the rectal dysfunction that commonly occurs in ATM. (5) He also had bladder dysfunction causing initial urinary incontinence, subsequent bladder spasms, and then urinary retention, which is found in 95% of patients during the acute phase of this condition. (4) He never had sensory impairment with a specific sensory level, although this is identified in only approximately 60% of children. (1) His symptoms reached nadir at day 11, with a rather abrupt onset of weakness that made the diagnosis more apparent.

This patient's presentation with LETM is not uncommon, with one study citing that most pediatric patients with ATM have LETM. (6) However, his spinal cord involvement of 20 vertebral segments from the cervicomedullary junction to the conus medullaris is far more extensive than in most patients. Studies show average involvement of 6 vertebral segments in children, and lesions in adult patients extend only 1 to 3 segments. (2)(7)(8)

Differential Diagnosis

Although findings from the history and physical examination can lead to a strong presumptive diagnosis, the differential diagnosis is broad, with ATM being a diagnosis of exclusion.

MRI is the most useful first step in evaluation because it can exclude noninflammatory diagnoses, such as compression or vascular disease. (7)(9) Cord compression from malignancy, disc herniation, or vertebral fractures can be directly visualized on MRI. Spinal cord infarction, especially when involving the anterior spinal artery, presents with sudden-onset weakness and sensory changes that may seem similar to ATM. However, spinal cord infarction can be distinguished by MRI, on which affected areas show diffusion restriction on diffusion-weighted imaging. (10) In addition, compressive and vascular etiologies typically have normal CSF findings.

If inflammatory myelopathy is visualized on MRI, it can be further divided into idiopathic and secondary ATM. Idiopathic ATM, as seen in this patient, is characterized by CSF pleocytosis and spinal cord inflammation on MRI. (7) Secondary ATM may be associated with infection, rheumatologic conditions, acute disseminated encephalomyelitis, neuromyelitis optica (NMO), or multiple sclerosis (MS). Several diagnostic studies may be obtained to help distinguish among these entities, including CSF studies (opening pressure, protein, glucose, cell count with differential count, viral studies, bacterial Gram-stain and culture, and oligoclonal bands), serum studies (complete blood cell count, blood culture, inflammatory markers, NMO antibodies, oligoclonal bands, dilute Russell viper venom time, rapid plasma reagin, Lyme disease enzyme immunoassay,

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antinuclear antibody, angiotensin-converting enzyme, Sjogren syndrome antibodies, and double-stranded DNA antibody), and neuroimaging. Acute disseminated encephalomyelitis can be differentiated from idiopathic ATM in that it often includes multifocal involvement on MRI (cerebral, cerebellar, optic nerve, and spinal cord). NMO may present as ATM and is specifically associated with LETM; however, most cases are positive for serum NMO antibodies. (6) MS-associated ATM can sometimes be distinguished with MRI brain findings, and it is generally associated with recurrent episodes of ATM. Interestingly, LETM is indirectly correlated with MS. (2)(11)(12)

Another important diagnostic consideration is Guillain-Barré syndrome (GBS), which can have a similar clinical presentation to ATM. However, MRI findings in GBS have more frequent enhancement of the spinal nerve roots as opposed to the cord, as seen in ATM, and the CSF in GBS demonstrates albuminocytologic dissociation with an elevated protein level without pleocytosis. (4) This patient's presentation is also similar to that of acute flaccid myelitis given the asymmetrical spinal cord dysfunction, primary acute motor deficits, minimal sensory involvement, and CSF pleocytosis. However, MRI findings in acute flaccid myelitis exhibit specific involvement of the anterior horn gray matter of the spinal cord. (13) This is in contrast to MRI findings in ATM, which can involve both gray and white matter and portions of the spinal cord other than the anterior horn, such as the posterior and central cord, as seen in this patient.

Patient Course

The involvement of his entire spinal cord, specifically the cervical spine, put this patient at risk for respiratory decompensation, so he was transferred to the PICU. There he received 5 days of intravenous methylprednisolone, the first-line treatment for ATM. He also required plasmapheresis, which is used in corticosteroid-refractory cases. (14) During this time he continued to have dysautonomic hypertension, and he was placed on nicardipine and nitroprusside infusions until his blood pressures normalized. Despite the extensive spinal cord involvement he did not require respiratory support. His pain was controlled with ketorolac, ibuprofen, and gabapentin. His increased stool burden was treated with a bowel regimen, and his urinary retention required an indwelling bladder catheter for 14 days. Physical and occupational therapy led to gradual improvement in his paralysis. At the time of discharge, 20 days after admission, his symptoms had fully resolved except for minimal left proximal weakness, for which he continued outpatient therapies.

Studies have shown that pediatric ATM has a better prognosis compared with adult ATM, often resolving within 3 months. In general, a poor prognosis is expected in patients younger than 3 years at onset and in those with rapid onset of severe neurologic dysfunction, such as severe muscle weakness, complete paraplegia, spinal shock, and respiratory failure. Delayed treatment, involvement of higher spinal lesions, and involvement of longer segments have also been associated with worse outcomes. (2)(8) Despite the presence of several unfavorable features, the patient described in this case had an excellent outcome, including early return of gross motor and bladder function and almost complete recovery by 2 months after discharge.

Lessons for the Clinician

- Patients with acute transverse myelitis (ATM) often present to their pediatrician's office with nonspecific symptoms of pain, urinary urgency, constipation, or weakness after a recent viral illness.
- ATM is a diagnosis of exclusion and the differential diagnosis is broad, necessitating a comprehensive evaluation, including laboratory tests and imaging.
- Diagnosis within 7 days of symptom onset is associated with better functional outcomes and overall quality of life. (2)

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Case 3: Pain and Weakness in a 12-year-old Boy

Hillary Seidenberg and Deepa Kulkarni

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4 Thrombocytopenia and Hematochezia in an Infant

Alexandra Schaller, DO,* Angela Myers, MD,† Shakila Khan, MD,‡
Avni Joshi, MD,§ Vilmarie Rodriguez, MD,¶ George Maher, DO**

*Division of Pediatric Critical Care, University of Tennessee Health Sciences Center, Memphis, TN
†Department of Medical Genetics, University of California Irvine, Orange, CA
‡Division of Pediatric Blood and Bone Marrow Transplantation, Mayo Clinic, Rochester, MN
§Division of Pediatric Allergy and Immunology, Mayo Clinic, Rochester, MN
¶Division of Pediatric Hematology/Oncology, Mayo Clinic, Rochester, MN
**Division of Pediatric Hematology/Oncology, Sanford Children's Hospital, Sioux Falls, SD

PRESENTATION

A 6-week-old white boy presented to his primary care provider with complaints of bloody stools and petechiae and was found to be thrombocytopenic, with an initial platelet count of $25 \times 10^3/\mu L$ ($25 \times 10^9/L$). The complete blood cell (CBC) count was otherwise normal. The mother's platelet phenotype was PLA1 positive, ruling out neonatal alloimmune thrombocytopenia. The infant's primary care provider recommended a milk and soy protein-free diet for the mother (the infant was exclusively breastfed), reasoning that the hematochezia and thrombocytopenia may have been unrelated. After this maternal dietary intervention, the infant's symptoms abated transiently.

Hematochezia, petechiae, and thrombocytopenia recurred at age 4 months, at which time the platelet count was $19 \times 10^3/\mu L$ ($19 \times 10^9/L$), prompting further evaluation. Medical history revealed spontaneous vaginal delivery at 39 weeks' gestation, mild eczema, and intermittent nasal congestion. The family history was significant for immune thrombocytopenia in his paternal grandfather in later adulthood but was otherwise noncontributory. Physical examination revealed height, weight, and head circumference to be normal. There was no evidence of dysmorphism. The patient was afebrile, with normal vital signs. Examination was remarkable for pinpoint petechiae involving the face, trunk, and lower extremities. There was no organomegaly or lymphadenopathy. The remainder of the examination findings were normal.

Evaluation included prothrombin time/partial thromboplastin time, fibrinogen, and ultrasonography of the abdomen, all of which were normal.

On review of the peripheral blood film, platelets were noted to be uniformly small. The mean platelet volume (MPV) determined on the CBC count was low at 7.3 fl (reference range, 8.5–12 fl) (Fig). Bone marrow evaluation revealed adequate numbers of megakaryocytes with normal morphology and was otherwise normal.

Because microthrombocytopenia can be associated with abnormalities in immunoglobulin (Ig) levels, these were measured and revealed an elevated serum IgA level of 141 mg/dL (reference range, 27–66 mg/dL); IgM was in the lower range of normal at 42 mg/dL (reference range, 40–143 mg/dL), and IgG was within normal limits.

AUTHOR DISCLOSURE Drs Schaller, Myers, Khan, Joshi, Rodriguez, and Maher have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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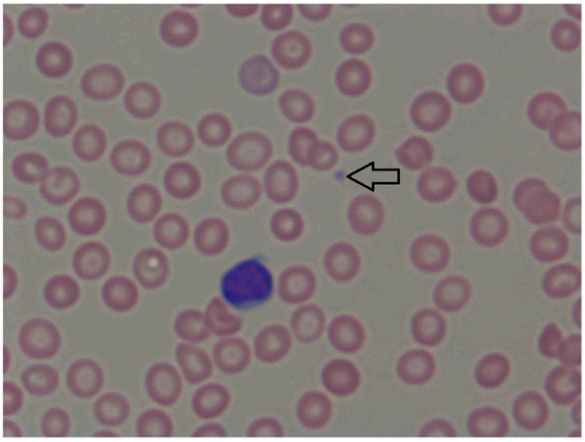

Figure. Peripheral blood smear from the patient. The arrow points to microthrombocyte.

The patient received 2 U of platelets, with an increase in platelet count to $143 \times 10^3/\mu L$ ($143 \times 10^9/L$) but with a gradual decrease to $29 \times 10^3/\mu L$ ($29 \times 10^9/L$) over 9 days. He remained platelet transfusion dependent, requiring transfusions for severe thrombocytopenia associated with hematochezia. By 5 months of age, refractoriness to platelet transfusions developed, which was unimproved with intravenous immunoglobulin but responded to oral corticosteroids, suggesting development of an autoimmune component.

Abnormalities of the peripheral blood morphology and MPV led to further testing, which proved diagnostic.

DISCUSSION

The finding of microthrombocytopenia prompted genetic evaluation for Wiskott-Aldrich syndrome (WAS), an X-linked disorder. A splice site mutation at Xp c.559+5 G>C (guanine to cytosine) was detected. A splice site is the location in a gene where processing of precursor RNA into mRNA takes place. (1) A mutation at this position generally has a profoundly negative effect on the synthesis and function of the protein produced. This mutation was confirmed, and expression of the WAS protein was measured in the patient's platelets and in donor lymphocytes, revealing a decreased ratio of 0.17 (reference range, 0.71–1.31). Genotyping of the mother was also completed, confirming carrier status.

The Condition

The *WAS* gene consists of 12 exons and 1,823 base pairs on the X chromosome, encoding 502 amino acids. (2) Expression is limited to hematopoietic cells. This protein is known to be involved in T-cell signaling and actin filament structure, contributing to megakaryocyte differentiation and formation of the immune synapse. (3) There is a large spectrum of phenotypes associated with mutations of the *WAS* gene ranging from isolated thrombocytopenia to the classic triad of thrombocytopenia, eczema, and immunodeficiency. Correlation of specific mutations and phenotypes has been reported, but many mutations have not been well characterized.

Management

The patient underwent stem cell transplant with a 10/10 human leukocyte antigen (HLA)–matched unrelated donor. Pretransplant conditioning consisted of busulfan, cyclophosphamide, and alemtuzumab. Tacrolimus and methotrexate were administered prophylactically to prevent graft-versus-host disease. The posttransplant course was complicated by the development of veno-occlusive disease, rotavirus infection, and *Clostridium difficile* colitis. Marrow engraftment was achieved 30 days after transplant, and the patient is now more than 400 days posttranplant with no evidence of WAS.

This case identifies a previously unreported mutation of the *WAS* gene with a severe phenotype requiring stem cell transplant. Previously, an individual had been reported with an alternate base pair substitution at the same locus who demonstrated a much milder phenotype.

Lessons for the Clinician

- The value of the peripheral smear review is illustrated by this case. Because mean platelet volume (MPV) is measured in the laboratory but not reported on the electronic medical record, the finding on the peripheral smear of small platelets was pivotal in the decision to review the MPV and to test for Wiskott-Aldrich syndrome (WAS), leading to early diagnosis, which likely contributed to successful transplant.
- Although rare, WAS should be considered in a male infant with unexplained thrombocytopenia; genetic testing is available commercially.
- Early diagnosis is valuable in WAS because these patients are susceptible to severe bleeding and infection. Also, allosensitization via multiple transfusions makes stem cell transplant more difficult.

References for this article are at http://pedsinreview.aappublications.org/content/40/5/254.

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Case 4: Thrombocytopenia and Hematochezia in an Infant

Alexandra Schaller, Angela Myers, Shakila Khan, Avni Joshi, Vilmarie Rodriguez
and George Maher

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Enthesitis-Related Juvenile Idiopathic Arthritis

Ayelet Rosenthal, MD,* Ginger Janow, MD, MPH†
*Department of Pediatrics, Rutgers University New Jersey Medical School, Newark, NJ
†Department of Pediatrics, Division of Pediatric Rheumatology, Joseph M. Sanzari Children's Hospital, Hackensack, NJ

Juvenile idiopathic arthritis (JIA) is defined as arthritis in children before their 16th birthday lasting for at least 6 weeks in the absence of another cause. The nomenclature surrounding chronic arthritis of childhood was revisited in the mid-1990s by the International League of Associations for Rheumatology, at which time the umbrella term *juvenile rheumatoid arthritis* was changed to *juvenile idiopathic arthritis*. In 2004, the International League of Associations for Rheumatology revised the previously defined 7 categories of JIA (Table 1), each with complex inclusion and exclusion criteria. Enthesitis-related JIA, or ERA, is the subcategory of JIA that can evolve into the adult form of ankylosing spondylitis; however, the differences in categorization between juvenile and adult forms of chronic arthritis are not clear-cut, and patients may be recategorized after their 16th birthday.

ERA affects approximately 10% to 20% of children with JIA. Hallmarks of disease include arthritis, defined as nonbony swelling or tenderness/pain on motion with limitation of motion, and enthesitis, defined as tenderness where the tendon or ligament inserts onto bone. Patients who have either arthritis or enthesitis, but not both, can also fall under the category of ERA if they have 2 of the other associated criteria (Table 2). Unlike many other autoimmune diseases, ERA has a male predominance (60%). The average age at diagnosis is 12 years, and most patients are either HLA-B27 positive (45%–88%) or have a first-degree relative with an HLA-B27–associated disease, including reactive arthritis, anterior uveitis, ankylosing spondylitis, or inflammatory bowel disease (20%).

The pathogenesis of ERA is poorly understood. A strong association with HLA-B27 has been established, yet it is still unclear how and to what extent HLA-B27 affects the onset and course of the disease. Overall, HLA-B27 positivity seems to portend a worse prognosis in patients in JIA, with greater disease activity and lower rates of remission. Recent data suggest that the microbiome may also have an important role in pathogenesis, but more studies are needed to clarify what this role might be.

At onset, in the first 6 months of disease, the arthritis is usually oligoarticular (≤4 joints) and asymmetrical. Joint involvement typically includes the sacroiliac joints, knees, ankles, and hip joints. Tarsitis, an inflammatory arthropathy of the midfoot, and sacroiliitis are extremely suggestive of ERA because they are much less common in the other forms of JIA. Cohort studies show that more than one-third of patients diagnosed as having ERA have sacroiliitis on radiographic imaging, many first presenting with low back pain.

Enthesitis presents as tenderness at the site of tendon or ligament insertion, most often but not exclusively in the lower extremities. Common sites include the quadriceps insertion onto the upper pole of the patella, patellar ligament

AUTHOR DISCLOSURE Drs Rosenthal and Janow have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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TABLE 1. Categories of Juvenile Idiopathic Arthritis

Systemic
Oligoarticular
Polyarticular, rheumatoid factor (+)
Polyarticular, rheumatoid factor (–)
Psoriatic
Enthesitis related
Undifferentiated

insertions on the lower pole of the patella and the tibial tuberosity, Achilles insertion onto the calcaneus, insertion of the plantar fascia onto the metatarsophalangeal joints, insertion of hip extensors on the greater trochanter, and common flexor and extensor tendons on the epicondyles of the humerus. Confusion may arise as apophysitis (including Osgood-Schlatter and Sever diseases) presents similarly, and deciding whether tenderness is from isolated apophysitis or is part of a larger autoimmune chronic inflammatory condition requires careful observation for other findings. Hence in patients with multiple sites of apophysitis, ERA should be considered as a possible diagnosis. Likewise, the presence of a red, painful, photosensitive eye may represent the anterior uveitis of ERA. Although the uveitis seen with oligoarticular JIA has an insidious, occult presentation, with ERA the onset is acute and typically unilateral, with a relapsing-remitting course.

ERA is diagnosed predominantly by clinical presentation. Laboratory tests and images are of low yield and are used only to help support the diagnosis. Complete blood cell count with differential count and inflammatory markers such as an erythrocyte sedimentation rate and C-reactive protein should be checked for all children with swollen joints. Inflammatory markers can be elevated or within normal limits. The presence of positive HLA-B27 can support the diagnosis, but absence does not exclude it.

As in all forms of JIA, plain radiographs are often negative at the time of diagnosis and are minimally helpful in determining active disease versus residual damage in a previously active joint. Radiographs are useful to look at the evolution of erosive disease and joint space narrowing over

TABLE 2. International League of Associations for Rheumatology Criteria for ERA

INCLUSION CRITERIA	EXCLUSION CRITERIA
Arthritis plus enthesitis	• Psoriasis or a history of psoriasis in the patient or a first-degree relative
OR	• Presence of immunoglobulin M rheumatoid factor on ≥2 occasions ≥3 mo apart
Arthritis or enthesitis plus ≥2 of the following:	• Systemic juvenile idiopathic arthritis
• Presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain	
• Presence of HLA-B27 antigen	
• Onset of arthritis in a boy >6 y of age	
• Acute (symptomatic) anterior uveitis	
• History of AS, ERA, sacroiliitis with IBD, reactive arthritis	
• Acute anterior uveitis in a first-degree relative	

AS=ankylosing spondylitis, ERA=enthesitis-related juvenile idiopathic arthritis, IBD=inflammatory bowel disease.
Reprinted from Gmuca S, Xiao R, Brandon TG, et al. Multicenter inception cohort of enthesitis-related arthritis: variation in disease characteristics and treatment approaches. Arthritis Res Ther. *2017;19(1):84. Creative Domain License: http://creativecommons.org/licenses/by/4.0/.*

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time. Effusions are sometimes evident on standard radiographs, but ultrasonography with Doppler is a better tool for identifying fluid and synovial inflammation in most joints and can show tenosynovitis. Although ultrasonography may also be able to identify enthesitis in some patients, its accuracy in children is controversial.

Musculoskeletal ultrasonography is an increasingly useful mode of assessment that does not involve radiation and can be performed at the bedside. Currently, it is an evolving technique, but it is user dependent, and no universally accepted scoring system has yet been developed for the pediatric population. Changes in the skeleton during childhood can make interpretation challenging and requires a detailed understanding of the stages of ossification.

Magnetic resonance imaging (MRI) is a sensitive tool for identifying synovitis and enthesitis, and the gold standard for sacroiliac imaging in both children and adults is MRI with short tau inversion recovery. Findings of sacroiliitis on MRI include sacral and ileal bone marrow edema with or without evidence of capsulitis or enthesitis. However, the cost of MRI and especially the need for anesthesia in many children limit its routine use in young patients.

Treatment for ERA deviates somewhat from the paradigm used for many other forms of JIA. Some evidence supports the use of a nonsteroidal anti-inflammatory drug as monotherapy, and in some cases that may control enthesitis in the absence of arthritis. Methotrexate, a disease-modifying antirheumatic drug used often as a first-line agent for other forms of JIA, has not been shown to be effective in treating axial disease but is sometimes useful for peripheral disease. Sulfasalazine may have some beneficial effect, but the data are sparse. Tumor necrosis factor α inhibitors are considered a first-line agent in patients with axial disease and may slow disease progression and improve symptoms.

Recognition of ERA is paramount for initiating early treatment and preventing long-term disability. The diagnosis of ERA should be carefully considered in patients with low back pain, morning stiffness, enthesitis, and a family history of HLA-B27–associated diseases. As our understanding of its pathology grows, we will hopefully be able to better collaborate with our adult counterparts to define, diagnose, and treat this disease that may evolve into adult forms of spondyloarthritis.

COMMENT: More common in children than ERA are the apophysitides Drs Rosenthal and Janow mention, particularly, Osgood-Schlatter and Sever diseases, but also so-called little league elbow. An apophysis is a bony outgrowth that serves as the site of attachment for a tendon or ligament. It has its own ossification center that, with maturity, fuses to its underlying bone; however, until that happens it remains vulnerable to injury, especially from overuse.

Osgood-Schlatter disease, painful inflammation at the insertion of the patellar ligament onto the tibial tubercle, affects children usually in their early teens who play sports that put stress on the knees. Similarly, Sever disease results from trauma at the insertion of the Achilles tendon onto the calcaneal apophysis from repeated stress to the foot. Repetitive throwing, especially pitching, puts stress on the elbow where the medial collateral ligament inserts onto the medial epicondyle. In fact, this overuse injury to the elbow of young baseball players has become so common that little leagues have instituted limits on the number of pitches a child can throw in a game.

– Henry M. Adam, MD
Associate Editor, *In Brief*

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Pediatric Osteoporosis

Coral L. Steffey, MD*
Department of Pediatrics, ECU Brody School of Medicine, Greenville, NC

Pediatric bone health is determined by genetics, diet, mobility, and exercise, but it can also be affected by medications and chronic disease. Although a diagnosis of osteoporosis may inspire thoughts of the geriatric population, some children are also vulnerable. Physicians providing care to both pediatric and adult populations should particularly note the major differences in the diagnosis and management of osteoporosis in children.

Pediatric osteoporosis is defined by the International Society for Clinical Densitometry based on 2 criteria. First is "low bone mineral content or bone mineral density." Children with bone mineral density of 2 or more standard deviations below average measured using dual-energy x-ray absorptiometry (DXA) have "low bone mineral content." DXA, which exposes patients to small doses of ionizing radiation, is the only current reference standard for assessing pediatric bone mineral density. A patient's measurement is compared with standards for age, sex, and body size, and the result is reported as a *Z* score, with a value of less than −2.0 being abnormal. Unfortunately, variability in radiologic technique, the multidimensional growth of bone in childhood, and normative data that inadequately account for bone changes caused by puberty or chronic disease all present challenges to reproducible and accurate interpretation of DXA in pediatric patients.

The second criterion required for diagnosis of pediatric osteoporosis is "the presence of a clinically significant fracture history," defined as at least 1 long bone fracture in the lower extremity, at least 2 long bone fractures in the upper extremity, or a vertebral compression fracture. Some physician discretion in applying this criterion is warranted, specifically in cases of concern for fragility or low trauma fractures. For example, an adolescent with a long bone fracture of the leg after, for example, a fall down a flight of concrete stairs would be significantly less concerning than a similar fracture after minimal trauma.

The incidence of pediatric osteoporosis is not known, likely due to a combination of historical differences in diagnostic criteria, previous lack of well-established DXA reference data, and the wide variety of factors that may contribute to the development of osteoporosis. Increased risk of low bone mineral density and fractures is found with a wide range of genetic disorders, chronic illnesses, and use of specific medications. Modifiable factors such as calcium and vitamin D intake, soda consumption, and weightbearing exercise also affect the potential for pediatric osteoporosis, and pediatricians should incorporate screening questions into health maintenance visits to help assess risk.

Bone fragility is an obvious concern in children with bone disorders such as osteogenesis imperfecta, but studies have also demonstrated increased fracture risk in patients with connective tissue disorders such as Marfan syndrome and Ehlers-Danlos syndrome. One factor contributing to osteoporosis in these patients may be decreased exercise or mobility. Other patients with a limited

AUTHOR DISCLOSURE Dr Steffey has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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ability to participate in weightbearing exercise, including those with cerebral palsy, muscular dystrophy, or spinal cord injuries, have lower bone density and increased risk of fractures. Weightbearing exercise confers a variety of health benefits, and 2 studies have suggested that introducing school-based daily exercise in healthy prepubertal children has the additional advantage of increasing bone accrual. Those with restricted mobility can similarly experience improved bone health through thoughtful physical therapy.

Vitamin D deficiency with resultant impairment in calcium absorption may lead to rickets and eventual osteoporosis. Although decreased availability due to minimal sun exposure, poor nutrition, eating disorders, and prematurity are possible causes, it is also important to consider chronic disorders associated with malabsorption of vitamin D as predisposing to osteoporosis. Patients with short gut syndrome, celiac disease, and cystic fibrosis generally are at risk for deficiencies in all fat-soluble vitamins, and patients with chronic kidney disease may develop secondary hypoparathyroidism with subsequent vitamin D deficiency. Medications for seizures affect vitamin D metabolism and calcium absorption, and higher doses and use of multiple antiepileptic drugs further increase the risk of osteoporosis. Empirical vitamin D supplementation is reasonable in children with these conditions and in those receiving medical therapy for seizures.

Chronic, systemic glucocorticoids also have a host of deleterious effects on bone, including interference with vitamin D metabolism, increased bone resorption, decreased bone formation, decreased calcium absorption, increased calcium loss, and decreased sex hormone production. Patients receiving long-term immunosuppression medications, such as those with cancer, autoimmune disease, and organ transplants, are at risk for osteoporosis. Unfortunately, the underuse of these medications and inadequate control of chronic inflammation also places children at increased risk for fractures. Inflammatory cytokines associated with chronic conditions such as rheumatologic disorders or inflammatory bowel disease can decrease bone production and increase resorption. Cytotoxic chemotherapy, corticosteroids, and radiotherapy used for the treatment of childhood cancers also have a harmful effect on bone mineral density and can be of particular concern in children who may already have increased fracture risk due to bone-infiltrating malignancies. Although use of these treatment modalities is deleterious to bone health, it remains preferable to the systemic and bone risks associated with inadequate treatment of these underlying conditions.

Children with type I diabetes, abnormal corticosteroid production, and disorders causing hypogonadism are all at increased risk for osteoporosis. Whereas these patients are typically already under the care of an endocrinologist, adolescents with exercise-related amenorrhea and Turner syndrome and those receiving depot medroxyprogesterone therapy are less commonly followed by these subspecialists and therefore should be monitored by their primary care physicians for fractures and the need for further evaluation and intervention.

Inherent difficulties exist in performing and interpreting pediatric DXA, and there is a lack of clear predictive value in children without significant fracture history. The American Academy of Pediatrics recommends DXA for children with clinically significant fractures and those with medical conditions that place them at increased risk for fractures. Specifically, DXA should be performed in pediatric patients with vertebral fractures, fractures out of proportion to the inciting trauma, and multiple long bone fractures. Although screening questions and counseling to prevent modifiable causes of osteoporosis are appropriate in all children, DXA is not indicated in otherwise healthy children. In all pediatric patients, therapeutic interventions should focus on addressing underlying etiologies of bone fragility.

The treatment team caring for a child with low bone density should optimize medical management of the underlying condition while simultaneously employing general strategies for improving bone health. For example, an adolescent with anorexia nervosa will have improved bone density with weight gain and return of normal estrogen production alone, and bone remineralization can be further augmented with supplementation with vitamin D and calcium. Bisphosphonates are not indicated to be appropriate for first-line use in otherwise healthy pediatric patients with low bone density. Use of bisphosphonates should be reserved for children with symptomatic or severe osteoporosis that is refractory to supplementation and management of comorbid conditions, and for conditions such as osteogenesis imperfecta where, despite disease management, recurrent painful fractures may be ameliorated and risk of vertebral collapse minimized.

Regardless of the source, pediatricians can ensure that all patients at risk for low bone mineral density have adequate vitamin D and calcium intake. Unfortunately, there are no standardized recommended daily allowances for children with these conditions, but adequate amounts recommended for healthy children should be a minimum expectation.

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Currently, adequate vitamin D intake for healthy infants younger than 1 year is 400 IU/d and for healthy children 1 year and older is 600 IU/d. Vitamin D levels do not need to be measured as a routine screening tool but are reasonable in children with a history of clinically significant fractures. Similarly, calcium intake in high-risk patients should at least match the recommended daily allowance for healthy children, which varies based on age. Consultation with a registered dietitian may be helpful for parents striving to optimize nutrition. Pediatricians should encourage and facilitate participation in weightbearing exercise; collaboration with pediatric physical therapists can help to safely maximize activity in children at higher risk for osteoporosis and fractures.

COMMENT: The field of pediatric bone health has rapidly expanded during the past decade. Pediatricians are a critical part of the health-care team in addressing preventive strategies. Studies have demonstrated that bone health in adulthood is affected by intrauterine factors such as maternal vitamin D deficiency, smoking, alcohol consumption, caffeine intake, decreased physical activity, intrauterine growth retardation, and maternal diabetes. The period of childhood, from infancy through adolescence, is critical for bone health because 90% of bone density is determined by the end of puberty. Hence, pediatricians have the important responsibility to counsel families and patients about the importance of vitamin D intake, calcium intake, and exercise. We all know some of the challenges of encouraging vitamin D and calcium intake for children. In one study it was noted that calcium intake by diet alone is approximately 50% of the recommended dietary allowance for girls. But asking specifics about what types of food and dairy products are eaten and the quantities is essential. And, when found not to be sufficient, encouraging other alternatives, such as calcium-fortified cereals, juices, other foods, and supplements. Pediatricians are also essential in coordinating the care of children with special health-care needs because bone health may not always be a primary concern through the lens of the subspecialists.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

Correction

An error appeared in the print version of the January 2019 review "Sleep-Disordered Breathing in Children" (Gipson K, Lu M, Kinane TB. *Pediatr Rev.* 2019 Jan;40(1):3–13. doi: 10.1542/pir.2018-0142). In the first paragraph of the "Physical Examination" section on page 6, the text should reference the Friedman scale instead of the Brodsky scale. The online version of the article has been corrected, and a correction notice has been posted with the online version of the article. The journal regrets the error.

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Pediatric Osteoporosis

Coral L. Steffey

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Currently, adequate vitamin D intake for healthy infants younger than 1 year is 400 IU/d and for healthy children 1 year and older is 600 IU/d. Vitamin D levels do not need to be measured as a routine screening tool but are reasonable in children with a history of clinically significant fractures. Similarly, calcium intake in high-risk patients should at least match the recommended daily allowance for healthy children, which varies based on age. Consultation with a registered dietitian may be helpful for parents striving to optimize nutrition. Pediatricians should encourage and facilitate participation in weightbearing exercise; collaboration with pediatric physical therapists can help to safely maximize activity in children at higher risk for osteoporosis and fractures.

COMMENT: The field of pediatric bone health has rapidly expanded during the past decade. Pediatricians are a critical part of the health-care team in addressing preventive strategies. Studies have demonstrated that bone health in adulthood is affected by intrauterine factors such as maternal vitamin D deficiency, smoking, alcohol consumption, caffeine intake, decreased physical activity, intrauterine growth retardation, and maternal diabetes. The period of childhood, from infancy through adolescence, is critical for bone health because 90% of bone density is determined by the end of puberty. Hence, pediatricians have the important responsibility to counsel families and patients about the importance of vitamin D intake, calcium intake, and exercise. We all know some of the challenges of encouraging vitamin D and calcium intake for children. In one study it was noted that calcium intake by diet alone is approximately 50% of the recommended dietary allowance for girls. But asking specifics about what types of food and dairy products are eaten and the quantities is essential. And, when found not to be sufficient, encouraging other alternatives, such as calcium-fortified cereals, juices, other foods, and supplements. Pediatricians are also essential in coordinating the care of children with special health-care needs because bone health may not always be a primary concern through the lens of the subspecialists.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

Correction

An error appeared in the print version of the January 2019 review “Sleep-Disordered Breathing in Children” (Gipson K, Lu M, Kinane TB. *Pediatr Rev.* 2019 Jan;40(1):3–13. doi: 10.1542/pir.2018-0142). In the first paragraph of the “Physical Examination” section on page 6, the text should reference the Friedman scale instead of the Brodsky scale. The online version of the article has been corrected, and a correction notice has been posted with the online version of the article. The journal regrets the error.

ANSWER KEY FOR MAY 2019 PEDIATRICS IN REVIEW

Infant Peanut Introduction Simplified: 1. D; 2. D; 3. C; 4. D; 5. D.
Allergy Testing and Immunotherapy: 1. C; 2. B; 3. E; 4. B; 5. C.
Immunodeficiency Disorders: 1. D; 2. D; 3. D; 4. B; 5. E.

Correction

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Visual Diagnosis

Melena in a 13-month-old Girl

Malinda Wu, MD,* Meghan Kessler, MD,† Brett W. Engbrecht, MD, MPH,‡
Mark Tulchinsky, MD,§ Michael M. Moore, MD,§ Chandran P. Alexander, MBBS, MD*

*Department of Pediatrics, Penn State Hershey Children's Hospital, Hershey, PA
†Department of Pathology, Penn State Hershey Medical Center, Hershey, PA
‡Department of Pediatric Surgery, Penn State Hershey Children's Hospital, Hershey, PA
§Department of Radiology, Penn State Hershey Children's Hospital, Hershey, PA

PRESENTATION

A previously healthy 13-month-old girl presents to the emergency department after a bowel movement with copious dark maroon blood with clots (Fig 1). She is fussy during the bowel movement, which is typical for her, and becomes pale thereafter. She does not have a history of constipation. On physical examination she is afebrile, mildly tachycardic, normotensive, and oxygenating well on room air. She is nontoxic appearing, pale, has a soft and flat abdomen that is nontender, without masses, and there is no anal fissure. She has a congenital nevus on her lower back.

Laboratory tests in the emergency department are notable for an elevated blood urea nitrogen level (24 mg/dL [8.57 mmol/L]) with a normal serum creatinine concentration (0.36 mg/dL [31.8 μmol/L]) and glomerular filtration rate (101 mL/min/1.73 m^2), microcytic anemia (hemoglobin level, 8 g/dL [80 g/L]; hematocrit, 24.7%; mean corpuscular volume, 69 fL), and unremarkable coagulation studies. Supine and lateral decubitus plain films demonstrate an unusual air-filled, mildly dilated bowel loop with some wall thickening in the middle abdomen. Ultrasonography of the abdomen demonstrates focally dilated loops of bowel in the right lower quadrant containing stool but no evidence of intussusception. A Meckel scan performed 6 hours after intravenous administration of ranitidine (2 mg/kg) shows abnormal small-bowel uptake in the left upper quadrant (Fig 2).

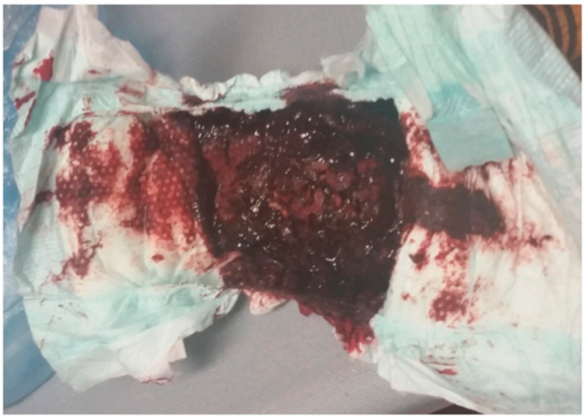

Figure 1. Patient's initial maroon-colored stool with clots.

AUTHOR DISCLOSURE Drs Wu, Kessler, Engbrecht, Tulchinsky, Moore, and Alexander have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

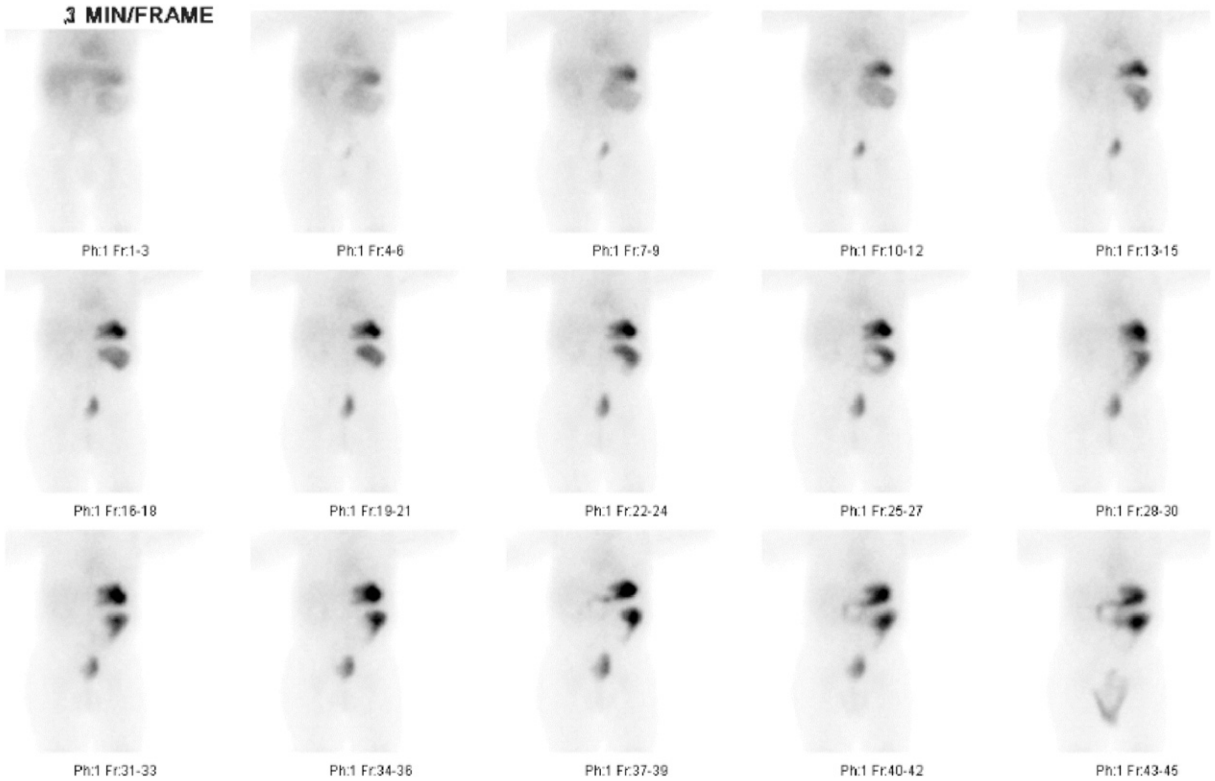

Figure 2. Patient's Meckel scan with abnormal uptake contemporaneous with gastric uptake in the left upper abdomen. Abnormal uptake occurs before radiotracer is seen emptying from the stomach into the duodenum (c-shaped loop connecting the stomach to the area of abnormal uptake).

DIAGNOSIS

A computed tomographic (CT) scan of the abdomen and pelvis reveals a well-defined tubular structure with an air-fluid level in the left upper quadrant corresponding to the abnormal uptake noted on the Meckel scan (Fig 3) and consistent with an intestinal duplication that is connected to the remaining bowel. Intraoperatively, a cyst measuring 4.7 cm is found to be attached to the mid-jejunum (Figs 4 and 5). There is an ulcer in the jejunum where the bowel lumen opens into the duplication cyst (Fig 6). Histology confirms that the muscularis propria is continuous from the jejunum to the duplication, which is lined with gastric epithelium (Fig 7). The ulceration of the jejunal epithelium has acute and chronic inflammation with fibrinous infiltrate (Fig 8).

DISCUSSION

The differential diagnosis for acute dark red rectal bleeding includes peptic duodenal ulcer, Meckel diverticulum, intussusception, lymphoid nodular hyperplasia, juvenile polyps, and, rarely, arteriovenous malformations.

In our patient, the elevated blood urea nitrogen level with normal serum creatinine concentration suggests increased enteral protein breakdown and absorption from an upper gastrointestinal bleed. The observed microcytic anemia suggests an additional chronic process, such as chronic occult gastrointestinal bleed, chronic inflammation, or iron deficiency anemia, rather than an acute gastrointestinal bleed, which would present with normocytic anemia.

GASTROINTESTINAL DUPLICATION CYSTS

Gastrointestinal duplication cysts are uncommon congenital malformations that are also called enteric or alimentary duplication cysts or simply duplication cysts. They have been inappropriately called abnormal Meckel diverticula, but they do not arise from the vitelline duct. They are thought to arise from abnormal budding of the embryonic foregut or abnormal recanalization of the embryonic bowel. Cysts have at least two layers: smooth muscle and a mucosal lining of gastrointestinal origin; they may also have intraluminal fluid, which may be seen on imaging as an air-fluid level. Rarely, duplication cysts may have respiratory epithelium. Most duplications are cystic, but some are tubular; some tubular duplications will connect proximally

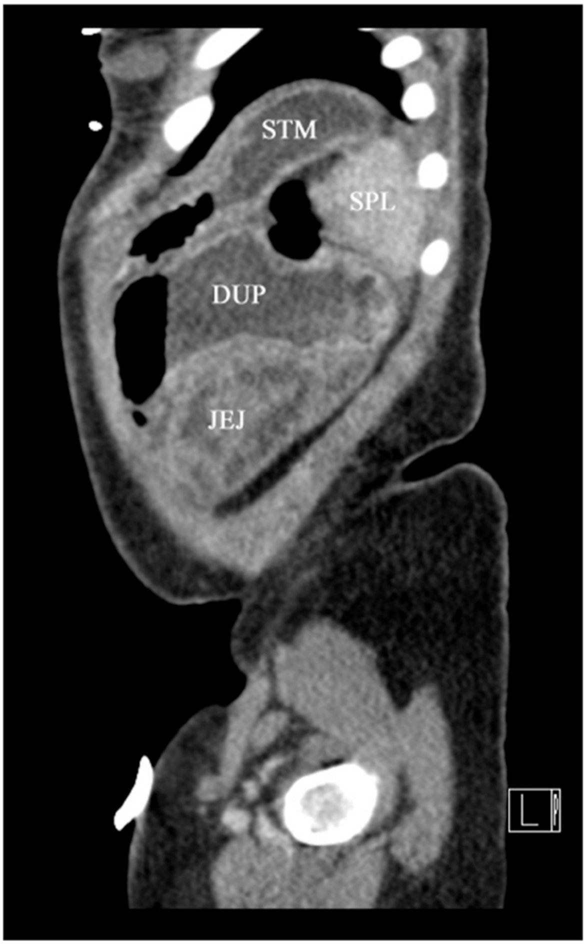

Figure 3. Patient's computed tomographic scan, sagittal view, showing a duplication cyst (DUP) and the adjacent stomach (STM), spleen (SPL), and jejunum (JEJ).

and distally to bowel and some will extend elsewhere, including the thoracic cavity. Gastrointestinal duplication cysts are named for the viscera they are adjacent to or contained within, not for the tissue they contain. Substantial variation has been found in the location of the cysts and their physical connection to the alimentary canal. Approximately half of them arise from the small bowel, and a few occur in extraintestinal locations such as sublingual or retroperitoneum.

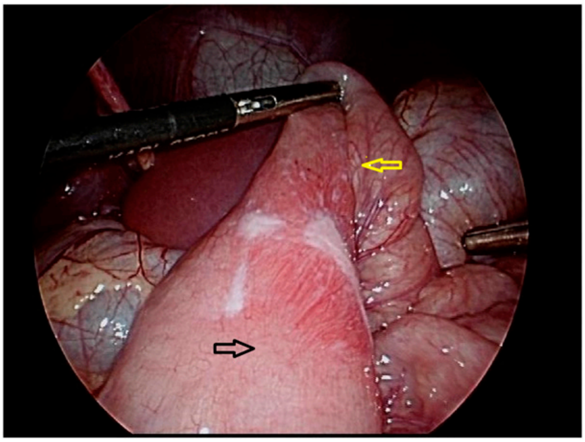

Figure 4. Intraoperative picture of a duplication cyst (black arrow) attached to the jejunum (yellow arrow).

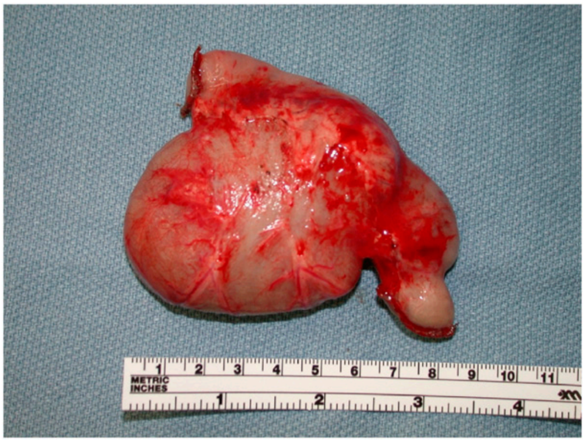

Figure 5. The resected cyst in the operating room.

The cyst may be distinctly separate from but near the gastrointestinal tract; the layer of smooth muscle may be contiguous with the alimentary canal with or without communication between lumens. Symptoms depend on the cyst shape, size, location, and connections to the alimentary tract. Duplication cysts can be asymptomatic and present as incidental findings during surgery or on imaging studies, or they may present earlier due to complications relating to mass effect (such as bowel obstruction or intussusception), bleeding (microcytic anemia, hemoptysis, hematemesis, or melena), ulceration, or cyst rupture. Most cysts present in infancy, but several case reports describe symptom onset in adulthood.

A duplication cyst without any communication to the bowel lumen may not be identified by endoscopy or

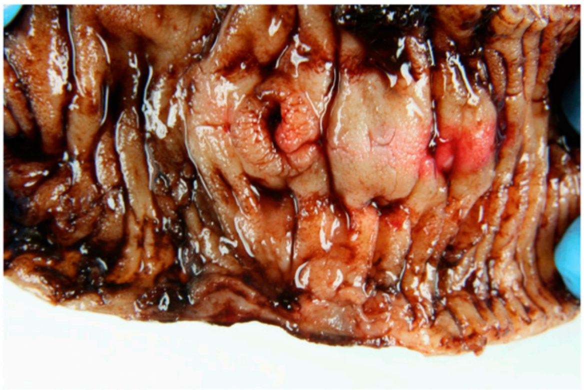

Figure 6. Gross pathology highlighting ulceration in the cyst.

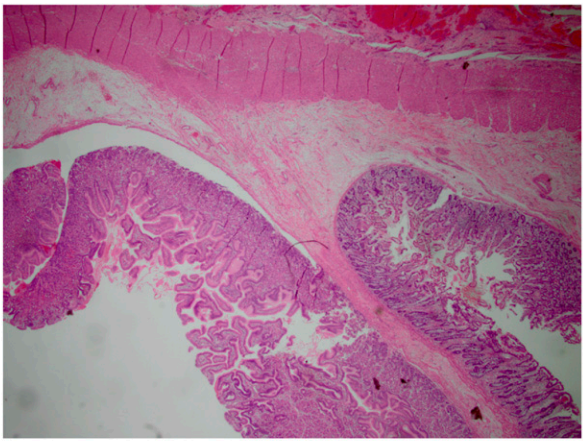

Figure 7. Histologic analysis of the cyst (hematoxylin-eosin stain, magnification ×20). Jejunum (right) and gastric duplication (left) interface. The muscularis propria is continuous from the jejunum to the duplication, with a layer of submucosa separating the intestinal and gastric epithelium approaching the orifice of the duplication into the small intestine.

fluoroscopic enteric contrast studies. Ultrasonography can diagnose duplication cyst by visualization of a cyst that is lined with intestinal wall, but this was not demonstrated in our patient, possibly due to overlying gas-containing bowel loops. The duplication cyst in our patient was detected by the Meckel scan because it contained ectopic gastric mucosa. A CT scan can confirm the diagnosis.

The bleeding patient must first be stabilized hemodynamically. In general, gastric and enteric duplication cysts are managed with surgical resection. Although some physicians advocate conservative management with observation for asymptomatic duplication cysts, this is not advisable due to risk of subsequent presentation with complications such as ulceration, bleeding, perforation, bowel obstruction, and, rarely, malignant transformation to adenocarcinoma in adults.

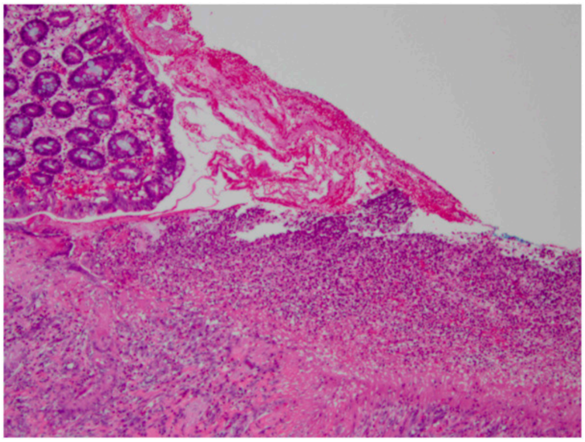

Figure 8. Histologic analysis of the ulcer in the cyst (hematoxylin-eosin stain, magnification ×40). There is ulceration of the jejunal epithelium with acute and chronic inflammation and fibrinous infiltrate.

PATIENT COURSE

The patient was stabilized with a transfusion of packed red blood cells. Once stabilized, the patient underwent a laparoscopic-assisted small-bowel resection, resection of the duplication cyst, and the primary anastomosis. She was discharged from the hospital after 2 days. She was evaluated 2 years later for an unrelated complaint and had no further symptoms related to her duplication cyst or surgery.

Summary

- A gastrointestinal duplication cyst has smooth muscle, mucosa of gastrointestinal origin, and luminal fluid. It can arise from any part of the gastrointestinal tract. It has been reported to present at any age but is more common in infants.
- Gastrointestinal duplication cysts with ectopic gastric mucosa can present with painless blood per rectum, mimicking a Meckel diverticular bleed.
- A Meckel scan may help identify ectopic gastric mucosa. If uptake occurs simultaneously elsewhere in the bowel along with gastric uptake, a duplication cyst lined with ectopic gastric mucosa should be considered, even if the uptake is not seen in the right lower quadrant, where Meckel diverticulum is typically located.
- The sensitivity of a Meckel scan using Tc99m pertechnetate to detect ectopic gastric mucosa may be increased by pretreatment with an antihistamine H2 receptor blocker such as ranitidine, which inhibits the secretion of pertechnetate from the gastric mucosa.

Suggested Readings

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Health Literacy: Implications for Child Health

Andrea K. Morrison, MD, MS,* Alexander Glick, MD, MS,[†] H. Shonna Yin, MD, MS[†‡]

*Section of Emergency Medicine, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI

[†]Department of Pediatrics and [‡]Department of Population Health, New York University School of Medicine/NYU Langone Health, New York, NY

Practice Gaps

Health literacy plays a critical role in the health of pediatric patients, with effects across the continuum of care (ie, preventive, acute, and chronic care). Although the use of health literacy–informed communication strategies and interventions can improve pediatric health outcomes and reduce health disparities, few providers receive training in health literacy principles, and few routinely incorporate health literacy–informed communication strategies into their daily practice.

Objectives

After completing this article, readers should be able to:

1. Understand how health literacy is a critical health concern for pediatric medicine.
2. Describe how low health literacy affects knowledge, behaviors, and health outcomes for parents, children, and adolescents in preventive, acute, and chronic care.
3. Recognize key strategies and interventions to improve communication and care in preventive, acute, and chronic care.

Abstract

Health literacy is an important issue to consider in the provision of health-care to children. Similar to the adult population, most parents face health literacy challenges. Of particular concern, 1 in 4 parents have low health literacy, greatly affecting their ability to use health information to make health decisions for their child. High expectations are placed on parents and children to achieve effective disease management and positive health outcomes in the context of complex health-care systems and disease treatment regimens. Low health literacy affects parent acquisition of knowledge, attitudes, and behaviors, as well as child health outcomes across the domains of disease prevention, acute illness care, and chronic illness care. The effect of low health literacy is wide ranging, including 1) poor nutrition knowledge and behaviors, 2) higher obesity rates, 3) more medication errors, 4) more emergency department use, and 5) poor asthma knowledge, behaviors, and outcomes. Health-care providers can

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ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
CDC	Centers for Disease Control and Prevention
ED	emergency department
OTC	over-the-counter

mitigate the effects of health literacy by seeking to align health-care demands with the health literacy skills of families. Effective health literacy–informed interventions provide insights into methods that can be used by providers and health systems to improve health outcomes. Health literacy–informed communication strategies should be used with all families in a "universal precautions approach" because all parents likely benefit from clear communication. As scientific advances are made in disease prevention and management, unless families understand how to follow provider recommendations, the benefit of these advances will not be realized and disparities in outcomes will be exacerbated.

INTRODUCTION

Health literacy is a key safety and quality issue to consider in the delivery of high-quality health-care by national organizations, including the Centers for Disease Control and Prevention (CDC), the Joint Commission, and the American Academy of Pediatrics. (1)(2)(3)(4)(5)(6) Health literacy, beyond the ability to read, is most commonly defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions." (4) Health literacy encompasses a complex set of skills, including knowledge, oral communication, written communication, quantitative ability, and navigation and information seeking (Table 1). (2)(7)(8)(9)(10) Every health-care encounter on the continuum from entry into the system to self-management at home requires health literacy skills. (11)

Health literacy issues are central to the interaction between individuals' capacities and the demands and complexities of the tasks placed before individuals by the health-care system. (12) Health literacy is, thus, not simply a description of one person's skills but also reflects the ability of a health system to meet the needs of consumers. There is a national movement toward establishing "health literate" organizations that take responsibility for making it "easy for people to navigate, understand, and use information and services to take care of their health." (12)

Individuals who possess limited health literacy skills, or who have low health literacy, have difficulty performing tasks necessary to maintain their health. For example, someone with low health literacy likely struggles with filling in basic information on medical forms, understanding diagnoses, taking medications correctly, adhering to recommended behaviors, and assessing the validity of and interpreting the content of health information presented via media channels. (2)(9)(13)(14) Research in adults has shown that individuals with low health literacy are less likely to use preventive services, have less knowledge of chronic illnesses and their management, have more preventable hospital visits, have more admissions and use of emergency services, are more likely to report their health status as poor, and have higher mortality rates. (2)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25)(26)(27) The construct of health literacy is linked to knowledge, self-efficacy, attitudes, health behaviors, and health outcomes (Fig). Although research findings related to children and adolescents who manage their own care is not as robust as that in adults, a growing body of literature suggests that children and adolescents who have low health literacy face similar problems as adults with low health literacy and may, additionally, be at a developmental disadvantage. (28)

It is important for providers to recognize that one cannot identify an individual as having low health literacy by appearance, although there are sometimes signs to suggest that an individual has low literacy (eg, incomplete intake forms, frequently missed appointments, not giving medications correctly, inability to give a coherent sequential history, or asks few questions to providers). (2) In addition, when considering the health literacy level of patients or parents, it is important to understand that health literacy is not a "fixed" trait. Factors such as stress and sleep deprivation can have a detrimental effect on an individual's health literacy, making communication and comprehension more difficult. Given provider difficulties in reliably judging an individual's health literacy level by appearance, as well as the potential fluctuation in skills based on circumstances, providers should use recommended communication strategies with all patients or parents, often referred to as a "universal precautions" communication approach. (29)(30)(31)

In this article, health literacy levels are described using the common terminology of low, marginal, and adequate. There are differences in how health literacy levels are

TABLE 1. Domains of Health Literacy and Examples of Health Literacy Skills (2)(7)(8)

SKILLS DOMAIN	EXAMPLES OF HEALTH LITERACY SKILLS[a]	EXAMPLES OF TASKS
Knowledge	Disease-specific knowledge	Albuterol is an inhaled asthma medicine that is used for the quick relief of symptoms
	Conceptual knowledge of health	Fever is a body temperature elevated from normal
	Vocabulary	Understanding words during oral or written communication enough to comprehend topic
Oral communication (listening, speaking)	Communicate history of illness or medical history	Give an accurate history of an acute problem or past medical problems
	Listen and comprehend	Understand the choices when spoken to about them
	Discuss risks, choices, treatments, and decisions regarding health	Participate in shared decision making regarding an upcoming procedure
	Ask for clarification and ask questions	Having the knowledge and skills to actively participate in conversations with a health-care provider
Written communication (reading and writing)	Reading and understanding written information	Brochures, facts sheets, booklets, or information using full sentences in paragraph form
	Interpreting and applying information needed to make health decisions	Understanding a brochure with a graph about body mass index and placing child's weight in a category and understanding meaning
	Understand and give consent	Comprehend required informed consent documents before procedure
	Interpreting a health-care document	Interpreting a food label to determine how many calories are in a food item
Quantitative	Interpreting and applying meaning of numbers (numeracy)	Understanding the normal range of a test
	Dosing medications (especially liquid medications, using inhaled medications, understanding timing)	Understand how to measure out the correct amount of medication and give it at the right times in the course of a day
Navigation and information seeking	Make, plan for, and get to appointments	Finding the way around the medical complex to get to a subspecialist's office
	Finding appropriate health-care providers	Navigate insurance and hospital systems to find the right doctor for child's problem
	Navigate insurance system	Call for prior authorization before procedure
	Finding information (online, print) needed to make health decisions	Being able to find pertinent and correct information about a health condition on the Internet, or in periodicals, books, or the media

[a] *This table is not an all-inclusive list of skills; illustrative examples of the concepts of health literacy skills are presented.*

described depending on the measure used, but we sought to interpret the health literacy levels in a consistent manner when presenting data.

EPIDEMIOLOGY

In the most recent report from the US Department of Education and the National Center for Education Statistics, 77 million adults, or 35% of the adult population, have low health literacy, (32) including 28% of US parents (>21 million). (9) It is important to note, however, that only 15% are categorized as having the highest level of health literacy skills, indicating that most individuals face some health literacy challenges. (9) Even more startling, only 8% of adults are categorized as having the highest level of health numeracy skills, or the ability to use numeric information to make health decisions. (33)

In the pediatric emergency department (ED) setting, the prevalence of parents and caregivers with low health literacy may be higher, with rates of up to 70%. (34)(35) This increased prevalence may be an indication of lack of health-care access due to poverty, language, or educational status, characteristics also associated with low health literacy.

Older adults, racial and ethnic minorities, people with low income levels, people with lower educational attainment, and nonnative speakers are among the

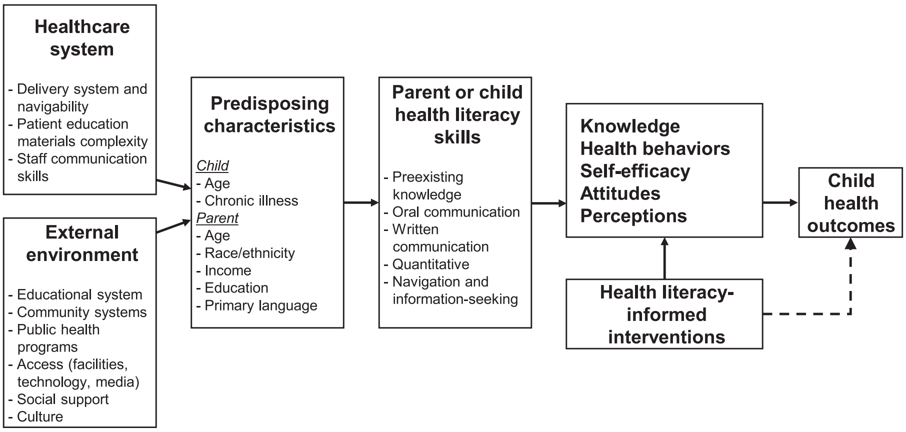


Figure. External factors, predisposing characteristics, and individual health literacy skills linked to knowledge, behavior, and health outcomes. (7)(8)(12)(36)

groups most likely to have low health literacy, (2)(37) and research suggests that health literacy is a likely mediator of income- and race/ethnicity-associated health disparities. (9)(38)

MEASURING HEALTH LITERACY

Rather than measure health literacy by screening individuals before care delivery, there is a general consensus that health systems should use a universal precautions approach to health literacy; this is championed by the Agency for Healthcare Research and Quality (AHRQ). (29) Universal precautions for health literacy advocate for communicating with all people as if they have low health literacy. Nearly all people benefit from strategies designed for those with low health literacy because health literacy skills can vary based on stress, sleep deprivation, pain, or disease-/context-specific knowledge.

In some instances, however, a clinician or researcher may desire to measure health literacy. Numerous assessment tools have been designed and are available to measure an individual's health literacy level (Table 2). To be suitable in a clinical environment, administration time must be short and content must be complex enough to accurately measure health literacy across the range of skills. The Health Literacy Toolshed is a comprehensive resource for health literacy measures (https://healthliteracy.bu.edu/).

COST

The estimated annual cost of low health literacy to the US economy is $106 billion to $238 billion, equal to 7% to 17% of personal health-care expenses. (39) In an analysis of nationally representative estimates, individuals with low health literacy spent an average of $500 more on office visits, $50 more on ED visits, and $2,600 more on prescriptions compared with those with adequate health literacy. (40) Another study found that patients with low literacy have higher annual costs ($8,000 higher, of which $6,000 reflect inpatient costs) than those with higher literacy, even after considering age, ethnic/racial group, and health status. (41)

The following sections discuss how health literacy affects knowledge, behaviors, and outcomes related to pediatric preventive care, acute care, and chronic conditions (summarized in Table 3).

PREVENTIVE CARE

Disease prevention by primary, secondary, or tertiary prevention strategies has transformed pediatric health. However, health system and public health efforts to prevent injury and disease require effective communication. Despite provider efforts and public health campaigns focused on preventive behaviors, many parents with low health literacy do not follow these recommendations, contributing to poor health outcomes.

Knowledge

Low health literacy has been associated with less injury prevention knowledge, including less knowledge on how to treat choking or what to do for a child if he or she is burned (2× the odds). (42) Expecting parents with lower health literacy faced with questions about prenatal screening for genetic defects had less knowledge of test availability and less understanding of test results than those with adequate health literacy. (43)

TABLE 2. **Health Literacy Measures and Characteristics**

MEASURE	MEASUREMENT DOMAINS	ITEM EXAMPLE	NO. OF ITEMS AND AVERAGE ADMINISTRATION TIME
Newest Vital Sign (44)	Written communication Quantitative	"If you eat the entire container, how many calories will you eat?" – referring to a nutrition label.	6 items, 3 min
Parental Health Literacy Activities Test (45)	Written communication Quantitative	"Using the instructions provided on the Enfamil powder formula, how much water and formula would you add to make a 4-oz bottle?" – referring to a label provided.	20 items, 21 min *Parental Health Literacy Activities Test 10:* 10 items, 13 min
Rapid Estimate of Adult Learning in Medicine (46)	Vocabulary knowledge Oral and written communication	Pronounce medical terms on a list correctly, eg, *flu, caffeine, menopause, osteoporosis, impetigo*	66 items, 2–3 min *Short form:* 7 items, 1 min *Teen form:* 66 items, 2–3 min
Single Item Literacy Screener (47)	Written communication	"How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?"	1 item, 1 min
Test of Functional Health Literacy in Adults (48)	Written communication Quantitative	"If you eat lunch at 12:00 noon, and you want to take this medicine before lunch, what time should you take it?" – referring to a medication label	67 items, 20 min *Short form:* 40 items, 7 min

Behaviors

Parents with low health literacy have less optimal health behaviors for injury prevention, including firearm safety–related measures (keeping a gun unloaded and locked in a safe place, discussing firearm safety). (42) Low health literacy is also related to other safety behaviors, including not having a working smoke detector (3× the odds), allowing a child to play alone near water (2× the odds), and having harmful household products and matches within reach (2× the odds). (42)

Several studies have found that parents with low health literacy have less optimal behaviors related to proper feeding and nutrition. Mothers with low health literacy exclusively breastfeed 20% less during the first 2 months of life (49) and have 2× the odds of feeding more formula than human milk. (50) Mothers with low health literacy have 2× the odds of feeding immediately when their child cries (rather than investigating other reasons for crying) and propping the bottle while their child feeds. (50) Low parent health literacy is also associated with 35% fewer parents using healthy weight behaviors with their child, such as increasing fruit/vegetable consumption, increasing physical activity, and decreasing fat intake. (51) Parents with lower numeracy skills have worse portion-size estimation skills, growth chart interpretation abilities, and nutrition label comprehension. (52) Parents with low health literacy also have fewer optimal physical activity–related behaviors, (42) including more infant television time and less tummy time. (42)(53) Sports participation is lower among adolescents with low health literacy. (54)

Low health literacy in parents or adolescents is associated with worse tobacco and alcohol-related behaviors. Children of parents with low health literacy have higher levels of salivary nicotine and air nicotine in the home. (55) Low health literacy was found to be a key predictor of tobacco use for adolescents (4× the odds). (56) In adolescent boys, low health literacy was associated with 2× the odds of consuming alcohol. (56)

Low health literacy in adolescents is significantly associated with increased violent behaviors. Specifically, after adjusting for sex, race, and age, those who have low health literacy have a significantly higher odds of carrying a weapon (2× the odds), carrying a gun (3× the odds), being in a physical fight at school (3× the odds), being in a fight that resulted in injuries requiring treatment (3× the odds), being threatened by a weapon at school (2× the odds), and missing school because of feeling unsafe (2× the odds). (57) Adolescents with low health literacy are more likely to be both the aggressor and the victim and less likely to only be a victim. (57)

TABLE 3. **Low Health Literacy and Relationship with Pediatric Health-Related Knowledge, Behaviors, and Outcomes**

	CATEGORY OF ISSUE AFFECTED BY LOW HEALTH LITERACY	DETAILS OF IMPACT OF LOW HEALTH LITERACY
Knowledge	Less topic-related knowledge	**Medication:** ↑ knowledge about use of cough/cold medications in a child <2 y, ↓ knowledge of weight-based dosing, ↓ medication label understanding **Asthma:** ↓ general asthma knowledge, ↓ knowledge of asthma treatment regimen and triggers, ↓ confidence in ability to manage asthma, ↑ perceived need for asthma medicine **Injury:** ↓ knowledge of choking treatment, ↓ knowledge of treating burns **Sickle cell disease:** ↓ sickle cell disease knowledge **Genetic screening:** ↓ knowledge of test availability and understanding of test results for prenatal screening for genetic defects
	Perceive child to be more ill	Perceive child to be sicker during mild acute illness
Behaviors	Worse safety behaviors	**Firearms:** ↓ safe firearm storage, ↓ discussion about firearm safety with child **Home safety:** ↓ safe water heater setting, ↓ working smoke detector, ↑ harmful household products and matches within reach, ↑ allow child to play alone near water
	Worse feeding, nutrition, healthy weight, and activity behaviors	**Nutrition and feeding:** ↑ formula-feeding (versus breastfeeding), ↓ feeding based on satiety cues (immediately feeds when child cries, ↑ bottle propping), ↓ portion size estimation, ↓ nutrition label comprehension, ↓ ability to assess portion size **Healthy weight:** ↓ ability to interpret growth charts, ↓ use of weight loss strategies (increasing fruits/vegetables, increasing physical activity, or decreasing fat intake) **Activity (parents):** ↑ child television viewing, ↓ adequate tummy time **Activity (adolescents):** ↓ sports participation
	Worse tobacco and alcohol behaviors	**Children:** ↑ exposure to second-hand smoke **Adolescents:** ↑ tobacco use, ↑ alcohol consumption (adolescent boys)
	Increased violent behavior	**Adolescents:** ↑ violent behaviors, ↑ weapon carrying, ↑ history of physical fights, ↑ likelihood of being aggressor and victim
	Incorrect medication use	**Over-the-counter medications:** ↑ difficulty understanding ↓ medication labels, ↑ errors in decision making based on age of use, ability to use active ingredient information in decision making **Prescription medications:** ↓ medication adherence (in general, epilepsy medication, glaucoma eye drops) **Liquid medications:** ↑ dosing errors (liquid medication), ↑ overdosing with dosing cup or dosing spoon
	Worse disease management	**Asthma:** ↓ likelihood of being seen by an asthma specialist, ↓ ability to use asthma action plan (eg, determine what zone asthma in, determine proper management) **Diabetes:** ↓ adherence to diabetes management (eg, insulin management, blood sugar monitoring, diet)
Outcomes	Greater prevalence of disease	**Obesity:** ↑ child obesity if parent with low health literacy; ↑ obesity if adolescent has low health literacy **Depression:** ↑ depression rate (worse child school readiness if parent has low health literacy and depression) **Behavior:** ↑ behavior problems
	Worse child disease-specific outcomes	**Asthma:** ↑ school days missed, ↓ asthma control **Diabetes:** ↓ glycemic control **Epilepsy:** ↑ seizure frequency **Nephrotic Syndrome:** ↑ relapse rate, ↓ complete remission rates
	Greater health-care utilization	**General population:** ↑ ED visits, ↑ nonurgent ED visits (among children without chronic illness)
	Worse health-care access	**Asthma:** ↑ ED visits and ↑ hospitalizations in children with asthma, ↓ rates of child health insurance

ED=emergency department.

Outcomes

Given worse knowledge and less advantageous behaviors, it translates that children of parents with low health literacy have worse health outcomes related to disease prevention. Health outcomes sensitive to health literacy include depression, school readiness, and having health insurance. Parents with low health literacy are more likely to have depression. (42) In a study of preschool-aged children, mothers with depressive symptoms and low health literacy were more likely to have children with worse school readiness and more behavior problems. (58) A child has 2.5× the odds of not having health insurance if a parent has low health literacy. (9)

Interestingly, if a parent has higher health literacy, their child is less likely to be vaccinated. (59) Parents with higher health literacy have more antivaccine attitudes and also perceive unofficial information sources to be more reliable if those sources oppose vaccines.

Interventions

To date, interventions using health literacy–informed strategies have improved care in 3 areas in preventive health: vaccine knowledge, child injury prevention knowledge, and obesity prevention. Health literacy–informed strategies incorporated by interventions include low grade-level readability, plain language, instructional graphics, bullet points, emphasis on key points, and clear layout. (60)(61)(62)

One study compared a vaccine information statement from the CDC and an easy-to-read intervention pamphlet and found that the pamphlet was preferred, was considered more readable, and was more easily understood. (60) Parents were able to comprehend only one-third to one-half of what they read despite most completing the 12th grade. The Safety in Seconds study, conducted with low-income, urban families, involved a computer kiosk placed in the waiting room of a pediatric ED, with intervention group parents receiving a customized child injury prevention report and control group parents receiving general child health information. (62) Participants with higher health literacy scores receiving the intervention were significantly more likely to have higher knowledge score improvements in poison storage and smoke alarms compared with those with lower health literacy levels. Although these strategies are meant to aid those with low literacy, these aforementioned studies found that the knowledge gains were greater in those with higher health literacy levels. (60)(62)

An obesity prevention study in low-income Hispanic families included in-person counseling in addition to the use of health literacy–informed print materials. (61) The intervention consisted of 1) individual nutrition and breastfeeding counseling, 2) support groups coordinated with well-child visits, and 3) plain language handouts using images and action-oriented, positive messages. Early findings include more floor tummy time and more unrestrained floor time in the intervention group. Study findings support the use of verbal counseling reinforced by consistent messaging in print materials as a more effective strategy than handouts alone.

ACUTE CARE

In pediatrics, where chronic illness occurs with a much lower prevalence than in the adult population, the health literacy challenges faced by parents in caring for their child's health needs often occur sporadically in the context of acute self-limited illnesses. Parents with low health literacy have a poorer understanding of acute illnesses and are less likely to search for information to guide their child's care. Parental decision making in the context of a knowledge-poor environment affects health-care utilization choices, including when and where to seek care, as well as appropriate medication use.

Knowledge

Parents with low health literacy have less knowledge of medications used during acute illness. Parents with low health literacy are more likely to report having difficulty understanding over-the-counter (OTC) medication instructions (3× the odds). (9) Parents with low numeracy skills are more likely to misinterpret OTC cough/cold medication labels and incorrectly decide that cough/cold medications can be used in a child younger than 2 years. (63) Parents with low health literacy are less likely to know that the dosing of a child's medication should be based on weight rather than age, increasing the likelihood of dosing errors. (64)(65)(66)

Furthermore, health literacy affects parents' ability to understand and interpret symptoms to make a health decision while their child is ill. Parents with low health literacy perceive that their child is sicker than parents with adequate health literacy during a mild acute illness. (67) Misinterpretation of child illness severity likely contributes to more ED visits during acute illnesses.

Behaviors

Frequently, OTC medications are used to symptomatically treat acute illness in children. Low health literacy limits parent ability to safely/effectively use these medications. Many parents, but especially those with low health literacy, do not use active ingredient information as part of decision making related to administering multiple medications, increasing the risk of multifold overdose. (68)

Low health literacy is associated with the use of nonstandard dosing tools (eg, kitchen spoons) and more parent dosing errors. (65) Parents with low health literacy made more large (>40% deviation) and small (20%–40% deviation) dosing errors compared with parents with adequate health literacy. (66) Parents with low health literacy also made more overdosing errors when using a dosing cup or dosing spoon. (66) Having both low health literacy and low English proficiency results in an even greater risk of dosing errors. (69)

Health literacy also affects how parents prefer to dose medications. Parents with lower health literacy prefer to use teaspoon units over milliliter units (3× the odds) and believe that a move to dosing in milliliters only (now recommended by the American Academy of Pediatrics) will be difficult (14× the odds). (70)(71)

Outcomes

Parent health literacy–related caregiving skills, including illness assessment and treatment skills, understanding of illness severity, and health system navigation, influence how parents with low health literacy seek care for their child during acute illness. (72) A child has 50% more ED visits if his or her parent has low health literacy, regardless of whether the child has a chronic illness. (34) Of children without a chronic illness, those whose parents had low health literacy had more than 3× the odds of presenting to the ED for a nonurgent visit, such as for a cold or a rash. (34) Also, children older than 2 years presenting to the ED with fever were more likely to have a nonurgent visit if their parent had low health literacy. (35)

Interventions

Acute care interventions have focused primarily on 2 key areas: medication dosing and ED use. Redesigning the process of provider medication counseling from a health literacy perspective has been found to decrease dosing error rates. Use of the HELPix intervention, which includes low-literacy pictographic patient- and medication-specific instruction sheets, along with optimized provider counseling (demonstration, teach-back/show-back) and provision of an oral syringe, was found to reduce liquid medication dosing error rates (control versus intervention: 48% versus 5% for daily-dose medications; 40% versus 16% for as-needed medications), in a randomized trial with a number needed to treat of 24. (73) The instruction sheets included a pictographic dosing diagram that visually showed the amount to measure in a recommended dosing tool. Several studies have demonstrated that medication labels with pictographic versus text-only instructions are more effective in reducing dosing errors. (73)(74)(75) Other considerations for dosing liquid medications include units of measurement and the size and type of dosing tools provided; a randomized study found that parents had fewer errors with milliliter-only instructions, that parents dosed more accurately with oral syringes (especially for smaller dose volumes), and that using a dosing tool size that more closely matched the dose volume prescribed led to fewer errors. (75) Provision of an optimized dosing tool benefited parents across health literacy levels, but especially those with low health literacy.

To reduce ED utilization, 2 studies used low literacy, easy-to-read health aid books that provided information on more than 50 common childhood medical problems. (76)(77) Parents participated in a 4-hour educational program on how to use the book and were given a copy to take home. In a primarily low-income minority population, there was a 30% reduction in ED use during a 6-month period, and in a Head Start population there was a 58% reduction in ED visits per child per year. (76) In another study designed to reduce ED use, intervention clinic patients who used a low-literacy health aid book were found to have fewer ED visits after implementation. (78)

CHRONIC DISEASES

Low parent health literacy has been linked to poor management and outcomes related to a child's chronic conditions. Many chronic childhood illnesses require that medications are taken daily, and these instructions can be difficult to follow, especially when titration of doses is needed to optimize care regimens. Children with chronic conditions may require frequent follow-up with their primary care provider or specialists, have specific dietary restrictions, or have other complex routines. The effect of low health literacy has been examined in the context of several common pediatric chronic conditions, including asthma, diabetes, obesity, and sickle cell disease.

Knowledge

Much of the work examining health literacy's impact on improving knowledge of chronic pediatric diseases has focused on asthma and sickle cell disease. Composite asthma knowledge scores (including information on asthma in general, treatment, and triggers) are lower for parents with low health literacy. (79)(80)(81) Parents with low health literacy are less confident in their ability to manage their child's asthma. (82) Low parent health literacy is also associated with increased worry about asthma and greater perceived need for asthma medicines. (83) One study also found lower sickle cell disease–specific knowledge in parents with lower scores on health literacy measures. (84)

Behaviors

Several studies have examined the relationship between health literacy and behaviors in parents whose children have chronic illnesses, including asthma. Children whose parents have low health literacy are less likely to receive care from an asthma specialist. (80) In 1 study, parents with low health literacy had more difficulty using asthma action plans to identify the level of control of a child's asthma (ie, which action plan color-coded zone the child was in) and determine appropriate management when given standard vignettes. (85)

Other studies have examined parental behaviors related to medication dosing and adherence for several chronic diseases. Parents with lower scores on a human immunodeficiency virus–specific health literacy assessment were more likely to make errors in dosing liquid zidovudine. (86) For parents managing complicated diabetes regimens, low health literacy is associated with low scores on a composite adherence measure (including insulin management, blood sugar monitoring, and diet). (87) Low parent health literacy is also associated with poor adherence to prescribed eye drops for glaucoma and epilepsy medications. (88)(89)

Outcomes

Children with chronic conditions whose parents have low health literacy have worse disease-specific outcomes and increased health-care utilization compared with those with adequate health literacy. Asthmatic children whose parents have low health literacy and numeracy scores have been shown to be more likely to be hospitalized (>4-fold adjusted incidence rate ratio). (81)(90) Asthma-related ED visits were more likely in parents with low health literacy in several studies (as high as 1.7× increased odds). (80)(81)(90) Low parent health literacy is associated with worse asthma control (both provider-reported and a validated parent-reported measure) (79) as well as more missed school days in asthmatic children (adjusted incidence rate ratio, 2.8). (81)

Studies assessing the relationship between parental health literacy and glycemic control in their type 1 diabetic children have shown mixed results. Lower scores on numeracy measures (91) and on the Newest Vital Sign health literacy assessment (92) are significantly associated with higher hemoglobin A_{1C} levels. In other studies, print literacy skills were not associated with glycemic control. (91)(93)

Both parent and child health literacy have been found to be related to weight outcomes. Parental low health literacy increases the likelihood of abnormal body weight in children. (94) Parents with low numeracy are more likely to have either underweight or overweight children. (52) Children and adolescents with low health literacy have a higher odds of obesity (up to a 5-fold increased odds) and increased body mass index Z score. (94)(95)

The relationship between health literacy and outcomes for several other diagnoses have also been studied. Seizures were more frequent in the setting of low parent health literacy in 1 study. (88) In children with nephrotic syndrome, higher health literacy scores were associated with a lower risk of first relapse (hazard ratio, 0.67) and higher odds of complete remission (2× the odds) in a clinic with standardized nurse-delivered medication. (96)

Interventions

Interventions geared toward improving outcomes in children with chronic diseases whose parents have low health literacy have focused on 2 primary health issues: asthma and obesity. One study assessed overall asthma knowledge scores in parents whose asthmatic children presented to the ED for evaluation of respiratory symptoms before and after they had received educational materials in video or written form. Absolute knowledge scores increased by 40% in parents with low literacy whether they received written or video education, whereas those with adequate health literacy had improved knowledge scores with video education only. (80) Others have studied the impact of a low literacy, photograph- and pictogram-based asthma action plan on parent asthma knowledge and provider counseling in hypothetical asthma counseling scenarios. Parents who received the low literacy plan were less likely to make errors in knowledge of medications to take every day and when sick (0.5× the odds) and errors regarding spacer use (0.1× the odds). (97) Physicians who counseled families with a low literacy plan provided more detailed and higher-quality counseling. (98)

Other recent literature has focused on health literacy–informed interventions to improve obesity-related outcomes. One quasi-experimental study, which focused on a community-based intervention applying universal health literacy precautions, led to improvements in child body mass index Z scores in obese children. (99)

COMMUNICATION STRATEGIES FOR PROVIDERS

Providers can mitigate the disparities in health knowledge, behaviors, and outcomes associated with low parent health literacy by using health literacy–informed counseling strategies as part of verbal and written communication with patients and families; such strategies are beneficial for individuals across health literacy levels. In this section, we discuss the theory and evidence behind several of these strategies, including data from adult studies (given that much of the evidence comes from the adult literature). A summary of health literacy–informed communication strategies is presented in Table 4.

Simplifying and Organizing Information

An overarching strategy to ensure that families understand information is to simplify the content as much as possible and organize it in a logical manner to reduce the cognitive load. The cognitive load, or the amount of mental demand that medical information presents, can affect how well an individual can process and understand this information. (100)(101) Per cognitive load theory, information that is too complex may not be fully processed or incorporated into working memory; use of more simple information can help reduce demand. (102)(103) Specific strategies are described in the following subsections.

Limiting Information. Limiting information presented to 3 messages (or the single most important message if possible) can make information easier to retain. Adults who are presented with shorter amounts of information that highlight key points and eliminate unnecessary information have better comprehension. (104)(105) Parents of children who are discharged home with more complex instructions (eg, multiple medications) have worse knowledge of their child's diagnoses, medication administration information, and appointments. (106) Complex instructions are also associated with failure to pick up prescriptions and attend appointments. (107)(108)

Focusing on key messages can help ensure that parents finish an encounter understanding the most essential information. (109) The "Ask Me 3" strategy does this by encouraging parents to ask "What is my main problem?" "What do I need to do?" and "Why is it important for me to do this?" In general, parents should be encouraged to ask questions to ensure that they understand the information presented.

Explicit and Action-Oriented Instructions. Focusing on specific behaviors can improve understanding. For example, the AHRQ-recommended Universal Medication Schedule provides actionable medication instructions in the context of 4 standard periods per day (eg, morning, noon, evening, and bedtime) instead of vague frequency information (eg, 2×, 4× per day). (110) Use of the Universal Medication Schedule has led to improved medication adherence, (111) and is preferred by patients. (112)

The best instructions also provide information salient to taking an action; excessive background information or explanations may be distracting. (113) Patients prefer more action-oriented instructions (114) and find them to be more understandable. (115)

Chunking. Chunking information into small, manageable pieces can help overcome the limits of working memory and reduces demand when there is a lot of information that must be learned. (116) Parents also prefer information to be broken down into pieces that are easy to understand, including for conditions such as diabetes when there are complex insulin regimens. (117)

Plain Language Verbal Counseling

Plain language verbal counseling refers to using simple words in short, simple sentences. Lay terms should be used, with minimal medical jargon. When jargon must be used, a full explanation in plain language terms should be included. Use of jargon and unfamiliar language contributes to misunderstanding or disregarding of advice. (116) Parents prefer that providers use plain language and avoid using jargon. (118)(119) Jargon can interfere with the communication process (120); for example, common diabetes jargon, such as "honeymoon period" and "peaks of insulin," were noted to be confusing for parents in 1 study, with parents with low health literacy disproportionately affected. (117)

Demonstration

Dual coding theory suggests that humans process verbal and visual information through separate channels, (100) so using both verbal communication and demonstration in providing instructions results in easier and quicker learning. (102)(103) Parents prefer demonstration of diabetes information over simple verbal instructions; this is especially true for parents with low health literacy. (117) Demonstrating how to dose liquid medications can lead to improved dosing accuracy. (121) Use of demonstration has also been incorporated into interventions that can improve proper dosing accuracy of liquid medications, as well as use of inhalers in asthmatic patients. (73)(122)(123)

Teach-back/Show-back

Because many families are not aware that they do not understand physician instructions, (124)(125) it is important to ensure that learning has occurred before ending the counseling encounter. One method of doing so is teach-back, where patients/caregivers state information that was taught to them in their own words. (29) Teach-back is considered a top safety practice by the AHRQ. (126) One

TABLE 4. **Health Literacy-Informed Communication Strategies**

STRATEGY	DEFINITION	RATIONALE	EXAMPLES OF STRATEGY
Simplifying and organizing information			
Limiting information	Providing only the minimal amount of information necessary	Per cognitive load theory, information that is too complex may not be fully processed into working memory	For a patient with multiple issues, counseling on single topic and emphasizing the key points during a clinic visit
Explicit and action-oriented information	Providing specific and nonambiguous instructions related to taking a particular action	Puts less strain on cognitive processes	Instructions stating to give medication "in the morning and in the evening" (as opposed to "twice per day")
Chunking	Breaking down information into segments that are easy to understand	More information can be stored in working memory when organized and sorted into chunks	A list of warning signs is grouped into 3 organ system chunks: 1) nausea, vomiting, diarrhea; 2) cough, trouble breathing; 3) pain, swelling, redness to make them easier to remember. Bullet points can be used to chunk written information
Plain language verbal counseling	Language that is clear, concise, well organized, and easy to understand for the intended audience	>40% of adults are categorized as having the lowest levels of health literacy. Many do not understand complicated medical terminology.	Discharge counseling incorporates simple terms such as *fast breathing* and *throwing up* (as opposed to *tachypnea* and *emesis*)
Demonstration	Showing a patient how to perform a certain task	Dual coding theory suggests that humans process verbal/visual information through separate processes; presenting information in a visual way makes verbal counseling more efficient	Showing a patient how to use an asthma inhaler with spacer
Teach-back	Having a patient summarize instructions in their own words	Restating small pieces of information leads to improved recall	Giving a patient medication instructions and having them say in their own words how they would measure out the medication
Show-back	Having a patient demonstrate how they would follow instructions you have explained	There is improved recall of information when you are asked to show how you would perform task. Provides opportunity for additional teaching if patient not able to demonstrate task.	Giving a patient medication instructions and having them show you how they would measure a dose using an oral syringe
Written information	Supplementing verbal counseling with written instructions to reinforce concepts	Using written materials can offset having too much information in working memory at a given time	Verbally discussing return to play guidelines after a concussion while also providing a written instruction sheet with the same information. These instructions should be written in plain language and in active voice, have a clear layout, and be written at a 6th grade or lower level. The written materials should have an evident purpose and use headers, captions, a font size of ≥12 points, and typographic cues (eg, bolding).

Continued

TABLE 4. (Continued)

STRATEGY	DEFINITION	RATIONALE	EXAMPLES OF STRATEGY
Pictographic and video instructions	Use of pictures or drawings to supplement written material	Dual coding theory suggests that humans process verbal/visual information through separate processes; multimedia theory suggests that some concepts are easily understood through visual compared with verbal/text-based instruction	A video or instruction sheet with step-by-step pictographic and verbal information to show a parent how to measure out a liquid medication.

helpful strategy to use when conducting teach-back is to create a shame-free environment by putting the responsibility of learning on the clinician. For example, “I want to make sure I did a good job of explaining how to give the asthma medication. Can you tell me how you would give Jennifer the medicine at home?” Cognitive science studies have shown that restating short amounts of information can lead to improved recall. (127)(128) In adult studies, use of teach-back has been associated with better glycemic control in diabetic patients (24) and improved understanding of discharge instructions. (129)(130)

Pediatric studies have found that families and providers believe that teach-back is effective, can improve communication, can confirm learning, and should be used as a communication technique. (131)(132)(133) Despite this, teach-back is not standard practice, with only 23% of physicians reporting that they routinely use this technique; barriers include limited time and volume of information to be communicated. (134)

Several interventions have been developed that include teach-back as part of a bundle of elements to improve outcomes. These intervention bundles led to improvements in rates of surgical site infections after spinal fusion procedures (135) and reductions in readmission rates. (136)

Another strategy that goes 1 step beyond teach-back is show-back, or having a patient demonstrate how they would follow physician instructions; in 1 study, more than 70% of patients with low literacy were able to teach-back medication instructions, but only approximately half of those were found to understand instructions correctly with show-back. (137) Another study showed that when providers asked children to show them how they would use an inhaler, the child was more likely to have a higher percentage of inhaler use steps performed correctly 1 month later. (138)

Written Information

It is well-established that supplementing verbal counseling with written instructions can help reinforce concepts. Written information should be up-to-date and reflect the language used during verbal counseling. The addition of written information may help overcome the limits of working memory; rather than having patients focus on trying to memorize multiple pieces of information at once, provision of written materials may help reduce the cognitive load. (139)

Studies have shown that parents who receive verbal and written instructions, compared with only one of these modalities, had higher levels of understanding of medication instructions and of the signs and symptoms associated with gastroenteritis. (140)(141)(142)

Although simply providing written instructions can help ensure learning, use of plain language written materials can further increase the effectiveness of communication. Plain language materials should include lay language and easy-to-understand terms, with action-oriented information written in short, simple sentences. Greater amount of white space and a clear organizational structure are also helpful for readers with low literacy. (143)(144) Although more than 40% of adults in the United States have the lowest levels of health literacy, (145) a large proportion of printed health information is written at a level higher than the average patient can understand. (147)(147) Experts recommend the use of educational materials written at a sixth-grade level or lower to ensure understanding, especially in low literacy populations. (116)

Interventions incorporating plain language written materials have been shown to improve parental understanding of medication instructions, reduce medication dosing errors, and ensure that parents are giving the prescribed number of medication doses. (73) Providers can get guidance on how to evaluate or develop low literacy materials using tools such as Doak and Doak’s Suitability Assessment of Materials checklist (116) or the AHRQ’s Patient Education Materials Assessment Tool. (148)

Pictographic and Video Instructions

Visually showing a patient or caregiver how to follow instructions is another beneficial communication strategy, which can be accomplished through the use of pictographic or video instructions. Multimedia or interactive modules should use the same language as provided in the written information. In addition to incorporating the concepts of dual coding theory mentioned previously, multimedia theory suggests that some concepts are too difficult to depict using text and verbal information alone and are most easily represented using multiple types of instructions, including visual representations, such as pictures and videos. (149) In adult studies, the use of pictographic instructions has led to improved understanding of instructions related to the care of lacerations, (150)(151) understanding of several aspects of medication labels, (152)(153)(154) and adherence to medications. (153)

Pictographic instructions have been shown to improve parent knowledge related to medication administration, understanding of asthma management, medication dosing and adherence, and instructions on preparation of oral rehydration solution. (73)(75)(97)(155) Diagrams and graphics incorporating key, limited amounts of information are easier to understand than more detailed diagrams. (156)(157)

Video instructions take the benefits of pictographic instructions 1 step further by giving step-by-step visual and verbal information. Demonstration of instructions can be provided in a standardized way and can be played back multiple times, without adding provider time burden. The use of educational videos can improve knowledge of asthma-related triggers and proper inhaler technique, and the understanding of several ED diagnoses. (158)(159)(160)(161)(162)(163)(164)

Summary

- Based on expert opinion, health literacy is defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions." (4)
- Based on quality observational studies, few US parents are categorized as having proficient health literacy, indicating that most parents encounter at least some health literacy challenges. (9)
- Based on quality observational studies on prevention, parents with low health literacy are less likely to observe injury prevention practices and follow recommended behaviors related to feeding and nutrition. Adolescents with low health literacy have worse tobacco- and alcohol-related behaviors and increased violent behaviors. (49)(51)(52)(53)(56)(57)
- Based on quality randomized controlled trials and observational studies on acute care, parents with low health literacy have worse knowledge related to medication use during an acute illness, make more medication errors, and are more likely to take their child to the emergency department. (9)(59)(60)(61)(62)(63)(64)(65)(66)(67)(68)(69)(70)(71)
- Based on quality observational studies on chronic care, parents with low health literacy have worse knowledge, health behaviors, and outcomes related to a variety of chronic illnesses, including asthma, diabetes, and obesity. (52)(79)(80)(81)(83)(84)(85)(86)(87)(88)(89)(90)(91)(92)(93)(94)(95)
- Based on quality randomized controlled trials, observational studies, and expert opinion, providers should consider use of the following evidence-based, health literacy–informed strategies to improve parent and patient outcomes: limiting information, explicit and action-oriented instructions, chunking, plain language verbal counseling, demonstration, teach-back/show-back, supplementing counseling with written information, and pictographic and multimedia materials. These health literacy–informed communication strategies should be used with all families in a universal precautions approach because all parents likely benefit from clear communication. (24)(29)(73)(75)(96)(103)(104)(105)(106)(107)(108)(109)(110)(111)(112)(113)(114)(115)(116)(119)(120)(121)(122)(123)(124)(125)(126)(127)(128)(129)(130)(133)(134)(135)(142)(143)(144)(145)(146)(147)(148)(149)(151)(152)(153)(154)(155)(156)(157)(158)(159)(160)(161)(162)(163)(164)

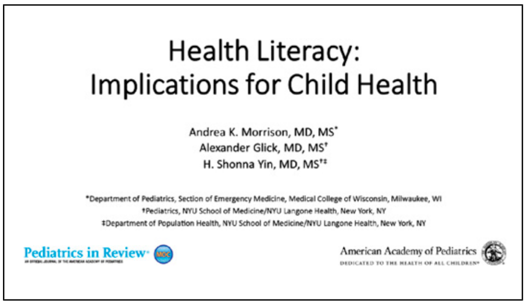
ADDITIONAL RESOURCES FOR PEDIATRICIANS

AAP Resources: Health Literacy and Pediatrics: https://www.aap.org/en-us/professional-resources/Research/research-resources/pages/Health-Literacy-and-Pediatrics.aspx

AAP Resources: Literacy and Health Literacy: Culturally Effective Care Toolkit – Chapter 6: https://www.aap.org/en-us/professional-resources/practice-transformation/managing-patients/Pages/chapter-6.aspx

MOC Health Literacy Activities Open Lines of Communication: https://www.abp.org/news/moc-health-literacy-activities-open-lines-communication

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/40/6/263.**



Health Literacy:
Implications for Child Health

Andrea K. Morrison, MD, MS*
Alexander Glick, MD, MS†
H. Shonna Yin, MD, MS†‡

*Department of Pediatrics, Section of Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI
†Pediatrics, NYU School of Medicine/NYU Langone Health, New York, NY
‡Department of Population Health, NYU School of Medicine/NYU Langone Health, New York, NY

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1. A hospital has adopted "becoming a health literate organization" as the central component of its safety and quality improvement programs. In considering the scope of its intervention strategy and to be most effective, hospital interventions should target which of the following patient populations or settings?
   A. All patients/parents (ie, universal precautions).
   B. Chronic care patients.
   C. Non–English-speaking patients.
   D. Suspected high-risk patients based on appearance.
   E. Preventive services/settings.
2. You discuss with a group of medical students the importance of health literacy and its correlation with health-care quality and safety. A medical student inquires about the reasons why institutions are placing such a heavy focus on health literacy. You explain to the student that based on the available evidence, higher health literacy rates have been associated with which of the following outcomes?
   A. Feeling unsafe at school.
   B. Higher health-care utilization costs.
   C. Higher rates of emergency department (ED) use.
   D. Higher risk of first relapse of nephrotic syndrome.
   E. Fewer hospitalizations in children with asthma.
3. In studying postdischarge ED visits and readmissions, a hospital quality and safety review committee identified medication dosing errors as a major cause in a significant percentage of these ED returns and readmissions. The committee started an initiative to address these dosing errors after discharge. Drug administration instructions provided at discharge in which of the following formats is expected to be the most effective evidence-based mitigating strategy that will lead to significant reduction in these medication administration errors?
   A. Based on total doses per day.
   B. Only provided in English language.
   C. Detailed instructions that are comprehensive in nature.
   D. Using a kitchen teaspoon for dose measurement.
   E. Using the Universal Medication Schedule strategy.
4. A 12-year-old boy newly diagnosed as having asthma is being discharged from the hospital after being admitted with asthma exacerbation. His medical history is significant for a few previous admissions for "bronchitis" and "pneumonia." No family history of asthma. On the day of discharge, the resident caring for the patient is explaining to him and his parents the discharge medications, which include an albuterol meter-dose inhaler to be used with an aerochamber and a mouthpiece and 2 more days of oral corticosteroids once a day. The patient has never used an inhaler before. Which of the following is the most effective method to use in providing this patient with instructions on the proper use of an inhaler?
   A. Develop a 7- to 10-task/step "to do" list for the family.
   B. Provide handouts with pictures.
   C. Provide only written handouts.
   D. Use of demonstration as part of verbal counseling, supplemented by written handouts with pictures.
   E. Use only verbal instruction.

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5. You are preparing a new information pamphlet on routine immunization for your practice. Considering the principles of health literacy, at which of the following maximum reading levels should this material be prepared to ensure understanding by all parents?

   A. 6th grade.
   B. 8th grade.
   C. 10th grade.
   D. 12th grade.
   E. College level.

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Sports Injuries

Nailah Coleman, MD*

The Goldberg Center for Community Pediatric Health, Children's National Health System, Washington, DC

Practice Gaps

1. Clinicians should be able to identify youth sports injuries predominantly by history.
2. Clinicians should be comfortable performing an appropriate physical examination in the evaluation of a youth sports injury.
3. Clinicians should be capable of ordering appropriate diagnostic tests in the evaluation of a youth sports injury.
4. Clinicians should be able to recommend a rehabilitation program and a return to play plan for a youth sports injury.
5. Clinicians should be aware of prevention strategies for youth sports injury.

Objectives After completing this article, readers should be able to:

1. Describe the epidemiology and risk factors for pediatric sports injuries.
2. Conduct a focused history about a pediatric sports injury.
3. Perform a focused examination for a pediatric sports injury.
4. Order appropriate diagnostic testing for pediatric sports injuries.
5. Elucidate key points on evaluation to formulate a diagnosis for pediatric sports injuries.
6. Develop a treatment plan for pediatric sports injuries.

It is well-known that daily physical activity supports a healthy lifestyle. One method for obtaining the recommended daily 60 minutes or more of vigorous physical activity for youth is sports participation, formal or informal.

Although the numbers have been increasing steadily over time, (1) approximately 60 million youth (age 6–18 years) are involved in some form of athletics (2) and approximately 44 million youth are in more than 1 sport. (2) In addition to the increased overall participation, the intensity of youth athletics has also increased. (1) Youth participants are younger than ever before, (1) and there are increased opportunities to participate in sports simultaneously. (1)(2) All of these issues have also created the opportunity for increased sports injuries in youth participants.

AUTHOR DISCLOSURE Dr Coleman has disclosed that she is member of the advisory board for the National Youth Sports Health and Safety Institute and the 2017 International Team Physician Course Faculty for the American College of Sports Medicine. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ACL	anterior cruciate ligament
CT	computed tomography
ED	emergency department
MRI	magnetic resonance imaging
OCD	osteochondral defect
OSD	Osgood-Schlatter disease
SCFE	slipped capital femoral epiphysis
SLJ	Sinding-Larsen-Johansson syndrome

Approximately 2.6 million emergency department (ED) visits each year are attributed to sports injuries in individuals aged 5 to 24 years, with the greatest percentage found in boys 5 to 14 years old. (1) The sports most commonly associated with ED visits include football, basketball, soccer, and cycling. (1) The most common injuries diagnosed in the ED (~20%–30% each) include sprains, fractures, and contusions. (1) Fractures are twice as common in boys; upper extremity fractures are more common than lower extremity fractures. (1) In fact, forearm, wrist, and hand injuries account for approximately 30% to 35% of the injuries seen in the ED, and the foot and ankle compose 20%. (1)

Not all athletic injuries present acutely. Athletes can also present with overuse or chronic injuries due to repetitive stress to a certain anatomical area without adequate recovery over time. (1)(2) In concordance with acute injuries, overuse and chronic injures have also increased over time. (1) Overuse and chronic injuries can also be attributed to issues with technique, poor athlete mechanics (eg, inflexibility), improper or inadequate coaching, and unconditioned or unmaintained equipment and training areas. (1) In addition, with the decreasing age of participants has come an increase in early sports specialization, (2) which exacerbates the cycle of overuse and chronic injuries.

Current recommendations to prevent overuse and chronic injuries in youth sports participation include incorporating 1 to 2 days off per week and 2 to 3 months off per year. (2) It is also recommended that athletes delay sports specialization until late puberty. (2)

UNIQUENESS OF THE PEDIATRIC ATHLETE

Although youth and adults all have the same basic body components, there are certain aspects of the youth athlete that can make them vulnerable to musculoskeletal injury. Because they are still growing, youth athletes possess open growth plates, which, as the weak link in the musculoskeletal chain, can more easily sustain injury, leading to disturbances of the growth plates, the apophyses, and the joint surfaces. (1) Osteochondroses are the bone-cartilage disturbances that can occur in youth athletes. (3) Although they have no known cause, their occurrence is potentially related to anatomical issues, rapid growth, vascular disturbances, acute or chronic trauma, and hereditary factors. (3) Apophysitis is one type of osteochondrosis that occurs at the attachment of a tendon to a bone with a secondary ossification center (apophysis) that becomes inflamed/irritated, (3) usually from chronic pulling or traction.

With the increase in youth sports participation and the variety of acute and chronic injuries that youth athletes can sustain, a pediatric provider's understanding of youth sports injuries, from history to treatment and prevention, will help young athletes continue to participate safely and effectively from young ages into adulthood.

GENERAL EVALUATION

History

When a young athlete presents to the clinic with a musculoskeletal concern, taking a good history can help lead to an accurate diagnosis and, thus, an effective treatment plan. Although they are extremely resilient, youth athletes can present with complaints from head to toe. Despite the variety of locations of discomfort, the important questions to ask about the nature of their pain are relatively constant. For example, if a youth athlete presents with back pain, a provider first needs to determine the exact location of pain (have them point with 1 finger), its character, whether it is acute or chronic, how long the pain has been present, and the frequency and intensity of pain episodes. (4) A reason for the pain is also helpful, including a description of the injury or inciting event for acute pain or a change in activity or activity level for overuse or chronic pain. (4) A provider should also determine the effect of the pain on the athlete's regular activities and athletics and what makes the pain better or worse. (4)

Some athletes can struggle with describing the mechanism of injury, particularly if the injury happened quickly during an athletic event. With the advent of small video cameras and cell phone video, however, there is a possibility that the injury episode is on video. Video might also help highlight a gross mechanical or training issue that may be contributing to or resulting from the athlete's pain. A Formal Motion Analysis is required for an in-depth and detailed evaluation of an athlete's mechanics.

When seeing a young athlete in the clinic, it is also important to ask about treatments tried or provided to the athlete before arriving at the clinic. Did he or she visit an ED or urgent care center? Did he or she work with the certified athletic trainer at school? Has he or she already tried physical therapy or chiropractic care? Were any of these previous services helpful?

Because not all pain is from an injury, acute or chronic, remember that athletes are humans, too, and can develop other conditions that can contribute to musculoskeletal pain, including tumors, rheumatologic conditions, and infections. (4) On review of systems, remember to ask about night pain, fever, weight loss, and morning stiffness. (4)

Examination

The provider should begin the physical examination by taking the injured athlete's history and observing the athlete's body position and ease of movement, (4) which can provide additional clues to the area of injury and the associated functional changes. After the history is completed, the anatomical area(s) of concern should be unclothed for observation, noting symmetry with the unaffected side, swelling, deformity, or skin disturbance. When conducting the examination, it is always important to assess the joints above and below the painful area because the athlete's concern may involve referred pain. (2) In addition to the ease of motion, a provider should also assess the range of motion of the area of concern, (4) noting deficiencies and in what direction of motion. The static (ie, ligaments) and dynamic (ie, muscles) joint stabilizers should be tested, (2) which will also assess other less evident injuries to the area and functional changes. The neurovascular status of the area should also be evaluated by checking pulses and capillary refill. (2) In youth athletes, one should assume a physeal injury if there is tenderness to palpation over the growth plate, even if the radiographs are negative. (1)

Diagnostic Testing

The most commonly used diagnostic study in evaluating musculoskeletal injuries is the radiograph, which helps to rule in or out a bony abnormality. (2)(3) Providers should consider obtaining images of the contralateral side if ipsilateral images raise the question of there being an anatomical variant versus a clinically relevant radiologic difference. (2)(3) Because radiographs are in only 1 plane, at least 2 views should always be obtained, typically anteroposterior and lateral.

Management

Unless noted later herein, most sports injuries benefit from a period of rest. Absolute rest, if a fracture is assumed or confirmed, involves immobilization of the area so as to prevent use. Conversely, relative rest involves simple avoidance of the offending activity. A period of immobilization, in a splint, cast, or brace, can be helpful for pain control and stability. Treatment with anti-inflammatory medications or analgesics and cryotherapy (ie, ice) can also help with pain control and swelling. (1) If a fracture has been ruled out and pain has resolved, a period of rehabilitation (at home or with a physical therapist) and a gradual return to activity can begin. Therapy considerations include stretching and strengthening exercises of the involved and coordinating muscle groups. (1)(2)(3)(4)(5)(6)

SPECIFIC INJURIES

Although it is important to understand the general evaluation and management of pediatric sports injuries, specific injuries to individual joints can require unique evaluation and management considerations, as indicated in this section and the Table.

Knee

Whereas upper extremity injuries present with greater prominence to the ED, outpatient pediatric providers are typically confronted with youth athletes with knee pain, both acute and chronic.

Acute knee pain in youth athletes can commonly present as patellar injury or anterior cruciate ligament (ACL) tear. Patellar dislocations, or lateral movement of the patella outside the femoral groove, typically occur with the femur in internal rotation and the foot planted. As the athlete contracts his or her quadriceps, the patella is pulled laterally. This injury is more common in female athletes 14 to 18 years of age. After acquiring a history with the mechanism noted previously herein, the examiner will note tenderness to palpation around the patella, particularly medially, and a positive apprehension test, a maneuver during which the examiner tries to pull the patella laterally, causing the athlete to be anxious that the injury is about to recur. Radiographs may reveal bony abnormalities, especially osteochondral defects (OCDs), caused by the bone-sliding-over-bone mechanism of injury. Because additional injuries are possible with a patellar dislocation, if it is suspected by history or examination, a magnetic resonance imaging (MRI) study should be obtained. After reduction, which usually occurs spontaneously or is completed in the ED, the knee should be immobilized for 2 to 3 weeks, allowing for weightbearing as tolerated. Rehabilitation and gradual return to activity can begin thereafter. Surgical referral should be considered for those with recurrent dislocations (15%–44%) or with bony abnormalities (eg, OCD) on imaging. Unfortunately, patellar dislocations tend to be associated with a decline in sports participation. (1) A more common injury with a mechanism similar to patellar dislocation is a patellar subluxation, an injury during which the patella slides laterally in the femoral groove but remains in the space. Athletes with patellar subluxations can present with the same symptoms of patellar dislocation. Depending on the athlete's current status, management may be similar to that of a patellar dislocation if the patient is more severely affected; if less severe, management may be typical for musculoskeletal disorders, as noted previously herein, (1) with the addition of the use of a patellar stability brace to help maintain the patella in the femoral groove.

TABLE. **Common Pediatric Sports Injuries**

INJURY	AGE AND SEX	SPORTS	MECHANISM	HISTORY	TREATMENT	EXAMINATION	TESTS
Tibial tubercle apophysitis (Osgood-Schlatter disease) (1)(2)	11–15 y M > F	Running, jumping, pivoting/cutting	Traction	Typically no injury	Relative rest, ice, NSAIDs; PT/rehab Patellar tendon strap	Tenderness and swelling and prominence of tibial tubercle ± pain with resisted extension	Radiographs not needed
Sinding-Larsen-Johansson syndrome (distal patellar pole pain) (1)(2)	10–14 y M > F	Running, jumping, kicking	Traction	Typically no injury	Relative rest, ice, NSAIDs; PT/rehab Patellar tendon strap	Tenderness distal patellar pole, otherwise normal	Radiographs normal versus irregularity at distal patellar pole
Patellofemoral pain syndrome (1)	F > M	Athletics with increased load at patellofemoral joint (eg, running, jumping, climbing stairs)	NA	Typically no injury	PT/rehab Arch supports for excessive pronators	Mild peripatellar discomfort, + patellar grind, otherwise normal	Radiographs not needed
ACL (1)	≥11 y 3–7× F > M	Multiple	Pivot/twist or hyperextension on landing	Pop with pain and instant swelling, no weightbearing, feels "unstable"	Surgery	Effusion, + Lachman test	Radiographs MRI (definitive)
Patellar dislocation (1) and patellar subluxation	14–18 y F > M	Multiple	Quadriceps contraction on an internally rotated femur with a planted foot pulls patella laterally; dislocation typically reduces spontaneously	Same as mechanism	Reduction for dislocation knee immobilizer, PT/rehab, surgery if recurrent or bony abnormality	Tenderness in peripatellar area (especially medially), + apprehension test, –Lachman test (similar mechanism to ACL)	Radiographs ± MRI
Calcaneal apophysitis (Sever disease) (1)(2)(3)	8–13 y M > F	Ground impact sports; athletes in cleats and gymnasts	Traction versus compression	Heel pain (especially with activity) (3)	Relative rest, ice, NSAIDs; PT/rehab heel cups	Pain with calcaneal squeeze, tenderness at Achilles insertion, Achilles tightness, weak dorsiflexion	Radiographs normal ± fragmented apophysis
Lateral ankle sprain (1)	All	Jumping, pivoting, uneven ground	Inversion	Rolled ankle	RICE Immobilize if suspected growth plate injury PT/rehab	Swelling and tenderness over affected ligaments, decreased range of motion	Radiographs (if skeletal immaturity, or meets Ottawa Ankle Rules if not)

Continued

TABLE. (Continued)

INJURY	AGE AND SEX	SPORTS	MECHANISM	HISTORY	TREATMENT	EXAMINATION	TESTS
Spondylolysis and spondylolisthesis (2)(4)	<16 y (spondylolisthesis)	Repetitive extension (throwers > rowers > gymnasts > weight lifters)	Repetitive spinal hyperextension	Low back pain ± radiate to buttocks or thighs, typically gradual, worse with extension and twisting, no neurologic symptoms	Relative rest PT/rehab Bracing is controversial spondylolisthesis > 50% or with neurologic symptoms or treatment failure, refer to orthopedics	Tight hamstrings, increased lumbar lordosis, + Stork test, ± tenderness in paraspinous area	Radiographs with AP, lateral, oblique views; oblique views with scotty dog sign with collar; ± MRI, single-photon emission CT or CT, bone scan
Low back strain (4)	All	All	Multiple	Typically acute	Relative rest Ice > heat massage NSAIDs Stretching	Negative straight leg raise (± back pain), normal neurologic examination	Radiographs if pain for ≥3 wk
Slipped capital femoral epiphysis (5)	11 y M > F Blacks > Hispanics > whites	All (obese)	NA	Hip, inguinal, thigh, or knee pain; limp ± pain	Immediate nonweightbearing surgical stabilization	External rotation at affected hip, antalgic gait, pain with/limitation of internal rotation	Radiographs of pelvis (AP and frog leg)
Legg-Calve-Perthes disease (5)	4–8 y M > F	All	NA	Limp without pain; knee pain (referred)	Conservative Surgery at discretion of surgeon	Pain with internal rotation in abduction; preference for external rotation	Radiographs
Hip apophyseal injury (1)(2)	10–25 y	Running, jumping, kicking, pivoting, twisting sport (eg, soccer, football, gymnastics, hockey)	Traction	Pain and popping	Rest, ice, crutches PT/rehab, surgery for 2-cm displacement or if failed conservative management	Swelling, tenderness, pain with active use of associated muscle or passive stretch	Radiographs to evaluate fragment displacement and to assess healing
Proximal humeral epiphysiolitis (Little League shoulder) (2)(6)	11–16 y	Baseball pitchers	Traction (torque)	Pain, arm fatigue, decreased speed and accuracy, (2) may have increased throwing program recently	Rest from throwing PT/rehab, appropriate pitch counts and rest	Tenderness proximal humerus, pain with resisted external rotation, ± decreased motion	Radiographs ± widening of physis; radiographs should include axillary view and view with humerus at 30° of external rotation, compare opposite side

Continued

TABLE. (Continued)

INJURY	AGE AND SEX	SPORTS	MECHANISM	HISTORY	TREATMENT	EXAMINATION	TESTS
Traumatic dislocation/ instability (shoulder) (1)(2)	Adolescents (males more likely to sustain recurrence)	Basketball, overhead throwing	Force applied with arm in abduction and external rotation	Same as mechanism	Immobilize initially PT/rehab to improve motion and strength surgery for athletes in contact sports	Shoulder asymmetry	Radiographs to evaluate fractures or other concomitant bony injuries
Multidirectional instability (shoulder) (1)	F > M	Gymnasts and swimmers	NA	Recurrent subluxation and spontaneous reduction	PT/rehab	Multiligament laxity	NA
Medial epicondyle apophysitis (Little League elbow) (1)(2)(6)	≤10 y	Throwing (especially pitching)	Traction versus avulsion	Pain worst at late cocking; decreased velocity/distance	Rest from throwing; PT/ rehab; surgical stabilization for >5-mm displacement; appropriate pitch counts and rest	Tenderness at medial epicondyle; pain with resisted wrist flexion and forearm pronation; pain with valgus stress	Radiographs (if mechanical symptoms, such as locking); compare opposite side
OCD (capitellum) (6)	> 10 y M > F	Throwers, gymnasts	Compression	Lateral elbow pain with throwing or weightbearing	Relative rest, surgery if unstable (ie, bony fragment or concern for dislodgment)	Decreased extension and supination/ pronation, effusion, potential mechanical signs/symptoms	Radiographs initially, although MRI demonstrates cartilage integrity/ surface
Distal radial epiphysitis (gymnast wrist) (2)	10–14 y	Gymnastics (especially, floor, beam, and horse)	Compression and shear	Participation in sport	Relative rest, ice, NSAIDs, wrist brace; PT/rehab	Normal motion, tenderness at distal radial physis	Radiographs with physeal widening

ACL=anterior cruciate ligament; AP=anteroposterior; CT=computed tomography; MRI=magnetic resonance imaging; NA=not available; NSAID=nonsteroidal anti-inflammatory drug; OCD=osteochondral defect; PT=physical therapy; rehab=rehabilitation; RICE=rest, ice, compression, and elevation.

With the increase in intensity of youth athletics, ACL tears are increasing in incidence. Their mechanism of injury mirrors, in part, that of patellar dislocation. Athletes will note pain and popping during a pivoting (ie, stop and twist) maneuver or with knee hyperextension on landing from a jump. Seventy percent of ACL tears are also accompanied by a meniscal tear; 46% occur with a cartilage injury. Tears of the ACL occur more commonly in those 11 years and older and in females (3–7 times) more than in males. (1) After the mechanism of injury noted previously herein, athletes will typically complain of immediate swelling, an inability to bear weight on the leg, and a feeling of instability. On examination they will have a large effusion and a positive Lachman test, (1) during which the knee is flexed to 20° to 30° and, with stabilization of the femur, the tibia is quickly pulled anteriorly to assess the ability of the ACL to stop the forward motion. A quick stop, or end point, signals that the ACL is intact; absence of the end point signals a concern that the ligament has been torn. Radiographs will demonstrate the effusion and may show medial tibial plateau injuries; however, the definitive test for an ACL tear is MRI. For athletes involved in pivoting sports, surgical intervention is necessary for ACL reconstruction. (1)

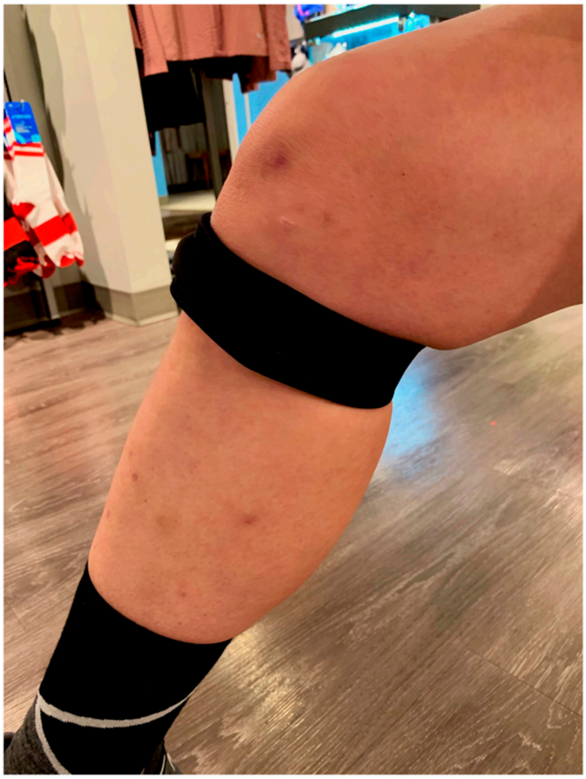

Figure. Patellar tendon strap placed above the tibial tubercle and below the patella.

Overuse and chronic knee injuries will also present to the pediatric clinic and typically involve the anterior knee. Chronic pulling on the tibial tubercle apophysis from the quadriceps via the patellar tendon can lead to tibial tubercle apophysitis, or Osgood-Schlatter disease (OSD). (1) Although it can occur in both knees, it is typically unilateral. (1) It occurs most commonly during periods of rapid growth (2) from 11 to 15 years of age. (1) Males are more commonly affected. (1)(2) Running, jumping, and pivoting, in other words sports that involve quadriceps contraction, can lead to or worsen this condition. (1)(2) Athletes in sports with these activities will often present with tenderness to palpation and swelling at the tibial tubercle, which may also be prominent on visualization. They may also experience pain with resisted extension (1) (ie, increasing the pulling forces on the tibial tubercle). Radiographs are not necessary to diagnose OSD alone. (2) Management is typical for musculoskeletal disorders, as noted previously herein, with the addition of the use of a patellar tendon strap to help offset the pulling forces on the tibial tubercle during athletics (Fig). (1)

Chronic pulling of the patellar tendon can also occur at its proximal attachment, resulting in distal patellar pole pain or Sinding-Larsen-Johansson syndrome (SLJ). (1) This syndrome occurs in slightly younger athletes (10–13 years of age) (1) and is more common in males. (2) Because it involves the same structures and a similar mechanism, commonly offending sports include those with running, jumping, and kicking. (1) On examination, athletes will have tenderness to palpation at the distal patellar pole. (1) Radiographs are often normal, but irregularity at the distal patellar pole can sometimes be seen. (2) Management is typical for musculoskeletal disorders, as noted previously herein, with the addition of the use of a patellar tendon strap to help offset the pulling forces during athletics. (1)

Patellofemoral pain syndrome is the name given to chronic anterior knee pain (1) that involves the mechanics of patellar motion in the femoral groove. Unlike OSD or SLJ, patellofemoral pain syndrome is more common in females, particularly in athletics that involve increased load at the patellofemoral joint; thus, running, jumping, and climbing stairs can all cause pain. Patellofemoral pain syndrome often occurs without injury or mechanical symptoms. On examination, athletes may experience mild peripatellar discomfort with palpation and present a positive patellar grind test, (1) during which the examiner slides the patella inferiorly toward the foot (with the knee in extension) and asks the athlete to contract the quadriceps muscle. A positive test will result in pain and a grinding sensation. (1) As referenced previously herein, when conducting the examination, it is always important to assess the joint above (ie, the hip for the knee) because the athlete's concern may involve referred pain (2) from the hip and be due to a slipped capital femoral epiphysis (SCFE, detailed later herein). Management is typical for musculoskeletal disorders, as noted previously herein. Arch supports may be useful for athletes with excessive foot pronation. (1)

Foot and Ankle

As noted earlier, athletes often present for care for foot and ankle injuries. These injuries are the second most common reason for youth athlete acute visits to their primary care physician. (3)

Two of the most common complaints seen in the pediatric clinic include calcaneal apophysitis and lateral ankle sprain. Chronic pulling of the Achilles tendon on the calcaneal apophysis results in calcaneal apophysitis or Sever disease. (1)(3) Unlike OSD, calcaneal apophysitis is often bilateral. (3) Athletes with calcaneal apophysitis are often younger than those with OSD, ranging from 8 to 13 years of age. (1)(2)(3) Males are more commonly affected. Commonly associated sports are those with significant ground impact forces, (1) such as those experienced by cleated athletes and gymnasts. (2) In the clinic, athletes may report heel pain, particularly with weightbearing activity. (3) On examination they may experience pain with calcaneal squeeze (medial and lateral compression at the growth plate) (1)(2)(3) and tenderness to palpation at the Achilles insertion. (3) They may also have tight Achilles tendons and weak dorsiflexion strength. (3) Radiographs are often normal, but irregularity at the calcaneal apophysis can sometimes be seen. (2) Management is typical for musculoskeletal disorders, as noted previously herein, with the addition of the use of heel cups to provide cushion and to mitigate compressive forces with weightbearing. (1)(2)(3)

A lateral ankle sprain, a stretch or tear of one of the lateral ligaments in the ankle, most commonly results from an inversion injury. (1) Sports that facilitate this motion include those with jumping, pivoting, and running on uneven ground. The most commonly affected ligaments are the anterior talofibular ligament and the calcaneofibular ligament. (1) Athletes will often present saying they "rolled their ankle." They may also note swelling and a popping at the time of injury, as well as an inability to return to the game and bear weight on that foot. On examination they will display swelling and tenderness over the affected ligaments, as well as decreased range of motion. (1) Radiographs should be obtained if the athlete is still skeletally immature or if the athlete's condition meets the Ottawa Ankle Rules criteria. (1) According to the Ottawa Ankle Rules, radiographs should be obtained if there is inability to bear weight at the time of injury or at the initial medical evaluation and if there is pain or tenderness at any of the bony prominences of the ankle/foot (ie, the tip or posterior portion of either malleolus, the base of the fifth metatarsal, or the navicular bone). Management is typical for musculoskeletal disorders, as noted previously herein, except for initial immobilization if a growth plate injury is suspected based on physeal tenderness on examination (even with negative radiographic findings, a Salter-Harris I fracture could be present). (1) Reassessment with a physical examination and imaging at 3 weeks can either rule out or rule in a fracture at that time, (1) and definitive treatment with casting can begin or rehabilitation with exercises and bracing can be initiated.

Back

Back pain is another common problem for youth athletes, be it from a bony or muscular injury. Fifty percent of adolescent athletes can present to the clinic with back pain. (2)(4)

Athletes involved in sports with repetitive extension (eg, throwers, rowers, gymnasts, and weight lifters) can experience a fracture of the pars interarticularis (2)(4) or spondylolysis. A pars fracture can be unilateral or bilateral; however, if bilateral, the absence of connection can allow the upper vertebral body to slip forward on top of the lower vertebral body, a phenomenon called spondylolisthesis. (2)(4) The percentage of slippage is graded in quarters from 0% to 100%. (2)(4) Spondylolisthesis is more common in athletes younger than 16 years. (2) Athletes with either condition will present to the clinic with low back pain that may or may not radiate to the buttocks or thighs. (2) Their gradually developing pain is worse with extension and twisting motions. (4) They deny neurologic symptoms. (4) An examiner might note increased lumbar lordosis, tight hamstrings, tenderness to paraspinous palpation, and a positive stork test, (2) during which the athlete stands, raises 1 knee, and extends the back. Increased pain on the symptomatic side is positive. Radiographs should include oblique views (taken at an angle to the patient's right and left), which may demonstrate a scotty dog with a collar (ie, the fracture site). (2)(4) Additional imaging with MRI, computed tomography (CT), single-photon emission CT (SPECT), or bone scan may be warranted. (2)(4) Management is typical for musculoskeletal disorders, as noted previously herein; however, bracing can also be considered but is controversial at this time. (2) Patients with spondylolisthesis and greater than 50% slippage (ie, grade III or IV) or neurologic symptoms and patients with either spondylolysis or spondylolisthesis and treatment failure should be referred to orthopedics. (4)

Six percent of athletes may present with a low back strain. (4) Although it causes pain, it is still a benign condition, and other, more concerning, diagnoses should be eliminated by history (as noted earlier) and physical examination. On examination athletes may note back pain; however, results of their straight leg raise should be negative and their neurologic examination normal. Radiographs should be obtained for athletes with pain lasting 3 weeks or longer. Management is typical for musculoskeletal disorders, as noted previously herein. (4)

Hip

Hip pain can occur in youth, be they athletes or not. In addition to a targeted history and physical examination, the age, sex, and health status of the athlete can help lead to the diagnosis.

Occurring in 10.8 per 100,000 children, the most common hip disorder in adolescents is SCFE, which occurs when the proximal femoral epiphysis slips posteriorly. (5) The incidence of SCFE hovers around age 11 years and is more common in males and in the black and Hispanic populations. (5) Although it can affect athletes in all sports, SCFE tends to occur in obese individuals, (5) so some sports may be more or less likely to have athletes presenting with SCFE. Affected athletes typically present with hip, inguinal, thigh, or knee pain and a limp. (5) On examination they tend to prefer keeping the affected hip in external rotation and have pain or limitation with internal rotation of that hip. (5) Because SCFE often occurs bilaterally, bilateral radiographs of the pelvis should be obtained and should include anteroposterior and frog leg views. (5) Management of SCFE varies from the typical musculoskeletal care that one would provide in the clinic. To prevent further injury to the joint, including avascular necrosis, cartilage damage, and later arthritis, these patients should be made nonweightbearing immediately and referred for urgent, if not emergency, surgical stabilization. (5)

Younger boys, aged 4 to 8 years, may present with hip pain due to avascular necrosis of the femoral head, also known as Legg-Calve-Perthes disease. (5) They also present with limping and may not complain of hip pain; however, they may experience referred pain to the knee. (5) On examination they also prefer to keep the affected hip in external rotation and experience pain with internal rotation in abduction. (5) Radiographs may demonstrate variable femoral head irregularity. Once identified, the appropriate management is without consensus (5); however, orthopedic referral is still warranted. Conservative care aims to reduce pain, improve motion, and prevent progression of any deformity; surgical care is determined individually by the surgeon. (5)

Older athletes, aged 10 to 25 years, (5) may experience a traction or avulsion injury involving any of the several apophyses located about the pelvis, including the anterosuperior iliac spine (origin of the sartorius), anteroinferior iliac spine (origin of the rectus femoris), ischial tuberosity (origin of the hamstring), and iliac crest (attachment site of the tensor fascia latae and abdominal muscles). (2)(1)(5) Sports that commonly involve a pull at the hip are those that include running, jumping, kicking, pivoting, and twisting, such as soccer, football, gymnastics, and hockey. (5) Typically, athletes will experience a sudden contraction that pulls at 1 of the apophyses, followed by a popping sensation or sound and pain. (1)(5) On examination they may have swelling and tenderness to palpation in the affected area, as well as pain with active use or passive stretch of the muscle in question. (1)(5) Radiographs can be helpful to evaluate the avulsed fragment displacement degree and to assess healing. (1)(5) Management is typical for musculoskeletal disorders, as noted previously herein, (1)(2)(5) with the consideration for orthopedic referral for 2-cm fragment displacement or failed conservative management. (1)(5)

Shoulder

Youth athletes in sports with overhead arm motion can present to the clinic with shoulder pain, both acute and chronic. The shoulder is the most commonly dislocated joint in adolescents, be it an acute or chronic dislocation. (1) Acute dislocations typically occur when a force is applied to the arm while the shoulder is abducted and in external rotation. (1) For example, a basketball player attempting a desperation long-distance (Hail Mary) shot before the buzzer has the ball knocked out of his or her hand during late cocking and feels pain in the shoulder. On examination these athletes' shoulders will appear asymmetrical due to the humeral head's new and abnormal anatomical location. (1) Radiographs should be obtained to evaluate for bony injuries, including fractures. (1) Once reduced, the shoulder should be immobilized in a sling. (5) Management is typical for musculoskeletal disorders, as noted previously herein, (1) with the consideration for surgery for athletes in contact sports due to a 65% to 75% chance of recurrence, particularly in males younger than 20 years. (1)

Female athletes tend more commonly to have multidirectional shoulder instability, which is a chronic, atraumatic condition commonly found in gymnasts and swimmers. (1) They will typically note recurrent episodes of subluxation with spontaneous reduction. (1) On examination they will demonstrate shoulder laxity anterior, posterior, or inferior to the glenohumeral joint. (1) In the absence of trauma (ie, no concern for bony injury), radiographs are not indicated. Management is typical for musculoskeletal disorders, as noted previously herein. (1)

Frequent throwers can present with proximal humeral pain caused by traction on the proximal humeral physis from the torque generated with throwing. (2)(6) Proximal humeral epiphysiolysis, or Little League shoulder, typically occurs in baseball pitchers aged 11 to 16 years. (2) In fact, one-third of baseball pitchers can experience shoulder or elbow pain, especially if throwing while fatigued or at higher velocities. (6) Athletes may present with shoulder pain, arm fatigue, decreased throwing speed or accuracy (2) and may report a recent increase in their throwing program. (6) It is important to query their throwing history: the amounts and frequencies of throwing events, participation on 1 or more than 1 team, and participation throughout the year or intermittently. (6) On examination, these athletes have tenderness to palpation at the proximal humerus, may have decreased shoulder motion, and note pain with resisted external rotation. (2)(6) Radiographs may demonstrate widening of the proximal humeral physis (2) and should include axillary views and anteroposterior views with the shoulder in neutral and in external rotation. (6) Imaging the opposite side can be helpful in the diagnosis. (6) Management is typical for musculoskeletal disorders, as noted previously herein, (2)(6) except for an initial, significant period of rest from throwing consisting of 6 weeks up to 3 months. (6) Various sports organizations, leagues, and medical organizations have posted recommendations for pitch counts and rest periods that adjust with age, (6) which can be helpful in counseling athletes and families in beginning or returning to baseball.

Elbow

The shoulder is not the only joint involved in throwing mechanics. Throwers also may present with elbow pain, medial and lateral.

When the flexor and pronator muscles of the forearm resist the valgus load associated with late cocking in throwing they generate a pull on the medial epicondyle. (1)(6) Some athletes may experience a sudden forceful throwing event, causing an avulsion of the medial epicondyle apophysis. (6) When the pulling is recurrent or becomes chronic, medial epicondyle apophysitis, or Little League elbow, can result. Commonly seen in those 10 years and younger, (1) baseball pitchers are most affected by Little League elbow. (6) Outside of a sudden avulsion injury, athletes with overuse or chronic pain will present with pain that is worst at late cocking. (6) As with Little League shoulder, they will also complain about their throwing ability, noting decreased velocity and distance. (6) They will have tenderness to palpation at the medial epicondyle (1)(2)(6) and experience pain with resisted wrist flexion and forearm pronation and with a valgus stress test. (2) Radiographs, with comparison views of the opposite side, should be considered, particularly if there are mechanical symptoms, such as locking. (6) Management is typical for musculoskeletal disorders, as noted previously herein, (2)(6) except for an initial, significant period of rest from throwing until pain free (1)(2)(6) and consideration of referral to orthopedics for surgical stabilization for avulsions that are displaced 5 mm or more. (6)

Although some athletes may experience medial elbow pain from pulling forces, others may experience lateral pain from compression forces, resulting in an OCD of the lateral capitellum. (6) These athletes tend to be older than 10 years and male, throwers and gymnasts. (6) They will present with lateral elbow pain with throwing or weightbearing and may demonstrate decreased extension, supination, and pronation (always compare with the unaffected side). (6) The examiner may note an effusion and mechanical signs, as well. (6) Although radiographs should be performed initially, an MRI most effectively demonstrates the cartilage surface and integrity. (6) Management is typical for musculoskeletal disorders, as noted previously herein, (6) except for consideration of referral to orthopedics for surgical stabilization if bony fragments are present. (6)

Wrist

As noted previously herein, upper extremity fractures are commonly seen in the ED. In the clinic, athletes may present with more chronic concerns. Fifty percent to 80% of gymnasts may sustain wrist injuries. With weightbearing on their upper extremities, gymnasts can sustain significant compression on and shear stress of the distal radial physis, resulting in distal radial epiphysitis, or gymnast's wrist. (2) Commonly seen in prepubertal athletes (aged 10–14 years), a gymnast's wrist is often associated with floor, beam, and horse activities. (2) On examination, athletes may display normal motion and experience tenderness to palpation of the distal radial physis. (2) Radiographs may demonstrate widening of the growth plate (2). Management is typical for musculoskeletal disorders, as noted previously herein, (2) except for the addition of a wrist brace as needed. (2)

CONCLUSION

As young athletes continue to increase their frequency and intensity of sports participation, so will their risk of injury increase. They will present to the ED but also to their primary care provider. Evaluation and management of common sports injuries in youth requires knowledge of the likelihood of injury in that age group, from prepubertal to young adult, or sex; the types of injuries associated with different sports; common mechanisms of injury that lead to young athlete pain; the anatomy of the area of concern; helpful historical and physical examination findings; and the appropriate diagnostic tests and therapeutic interventions, based on all of the above.

Summary

- Based primarily on consensus, owing to lack of relevant clinical studies, important historical findings to note in evaluating a pediatric musculoskeletal injury include confirming the location of the pain and the mechanism of injury, as well as performing a review of systems to rule out medical or rheumatologic causes of musculoskeletal pain.
- Based primarily on consensus, owing to lack of relevant clinical studies, important examination findings to note in evaluating a pediatric musculoskeletal injury include inspection of the area of concern at rest and with motion, as well as evaluating the ligament and muscle function of the affected area.
- Based primarily on consensus, owing to lack of relevant clinical studies, important considerations in ordering diagnostic testing to evaluate a pediatric musculoskeletal injury include obtaining radiographs with at least 2 perpendicular views to rule in/out bony abnormalities and loss of function.
- Based primarily on consensus, owing to lack of relevant clinical studies, important considerations in treating a pediatric musculoskeletal injury include setting a period of rest that allows for appropriate healing; prescribing orthotic devices to aid in pain control, movement, or recovery; prescribing a rehabilitation program for home or at a physical therapy center; and determining return to activities when the athlete has resumed full function of the affected area.
- Based primarily on consensus, owing to lack of relevant clinical studies, important considerations in referring to orthopedics for a pediatric musculoskeletal injury include significant structural or functional disability and failure of conservative management.

SUGGESTED QUALITY IMPROVEMENT PROJECTS

- Using a template to obtain an appropriate history and physical examination in evaluating a pediatric sports injury
- Creating decision support to order appropriate diagnostic testing in evaluating a pediatric sports injury

ADDITIONAL RESOURCES

For families:

- American Orthopaedic Society for Sports Medicine Stop Sports Injuries: https://www.stopsportsinjuries.org
- US baseball pitch counts: http://m.mlb.com/pitchsmart/pitching-guidelines/

For providers:

- Physical examination how-to videos by Dr. Jordan Metzl: http://drjordanmetzl.com/pediatric-exams/
- Team Physician Consensus Statements: https://journals.lww.com/acsm-msse/pages/collectiondetails.aspx?TopicalCollectionId=3

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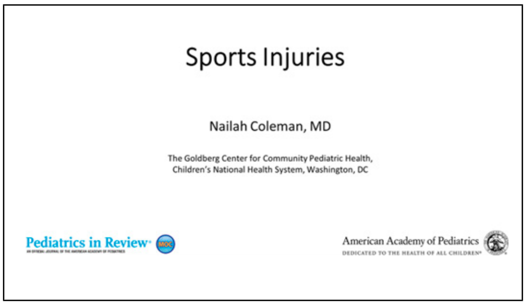

Sports Injuries

Nailah Coleman, MD

The Goldberg Center for Community Pediatric Health,
Children's National Health System, Washington, DC

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1. A 14-year-old girl is brought to the office after sustaining a twisting left knee injury while playing soccer. She is unable to bear weight and says that her knee feels unstable. She walks into the office with crutches. Physical examination of the left knee is significant for a large effusion and a positive Lachman test. An anterior cruciate ligament tear with or without meniscus involvement is suspected. In addition to placing her in a knee immobilizer, which of the following is the most appropriate next step in management?
   - A. Continue to use the crutches and reevaluate in a few weeks, after the effusion is resolved.
   - B. Order radiographs and magnetic resonance images of the knee and refer her to orthopedics.
   - C. Prescribe nonsteroidal anti-inflammatory drugs (NSAIDs) for 2 weeks.
   - D. Refer her to physical therapy.
   - E. Refer her to the emergency department for further evaluation.
2. A 12-year-old boy who runs track is brought to the clinic for evaluation of left knee pain. He has been complaining of left knee pain on the anterior tibia area below the patella. There is no swelling of the left knee or effusion. A swelling in the area of the anterior tibia directly below the left patella is noted. Which of the following is the most likely diagnosis of the left lower extremity in this patient?
   - A. Anterior cruciate ligament tear.
   - B. Patellar dislocation.
   - C. Patellofemoral pain syndrome.
   - D. Sinding-Larsen-Johansson syndrome.
   - E. Tibial tubercle apophysitis.
3. A 9-year-old boy who is a gymnast is brought to the clinic for evaluation of heel pain. The patient complains of bilateral heel pain, particularly when he lands on his feet during gym practice. He denies any recent trauma. On physical examination he has point tenderness around the midfoot area and pain with calcaneal squeeze bilaterally. No ankle swelling is noted. Which of the following is the most likely diagnosis in this patient?
   - A. Hypermobility syndrome.
   - B. Lateral ankle sprain.
   - C. Pes planus or flat feet.
   - D. Sever disease or calcaneal apophysitis.
   - E. Shin splints.
4. An overweight teenage female athlete is seen in the clinic because of low back pain. The patient participates in weight lifting. She reports on and off nonradiating lower back pain exacerbated by exercise and relieved by rest. There is no history of change in bowel habits and no urinary retention. On physical examination she does not have any midline back point tenderness and has normal neurologic examination findings, with no pain on straight leg raise. Radiographs of the lumbar spine are normal. The patient was recommended rest, ice, and NSAIDs. In addition to discussion about weight management, which of the following is the most appropriate next step in the management in this patient?
   - A. Complete bed rest.
   - B. Magnetic resonance imaging of the lumbar spine.
   - C. Myelogram.
   - D. Putting her in a back brace.
   - E. Reassessment in 3 weeks and possible physical therapy.

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5. A 13-year-old overweight boy is seen in the clinic with a history of intermittent bilateral hip pain, worsening during the last 4 weeks. The pain is exacerbated by running, and sometimes he feels that his legs will give away. This has affected his sports participation. He has limited internal rotation of both hips. Which of the following is the most likely diagnosis in this patient?
   - A. Back injury leading to referred pain to the hip.
   - B. Bilateral avulsion injury of the anterosuperior iliac spine.
   - C. Bilateral femoral anteversion.
   - D. Bilateral slipped capital femoral epiphysis.
   - E. Legg-Calves-Perthes disease.

Sports Injuries

Nailah Coleman

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Common Conditions Requiring Emergency Life Support

Kelsey Fawcett, MD,*† Nicole Gerber, MD,*† Shweta Iyer, MD,*† Guillermo De Angulo, MD, MPH,*†
Martin Pusic, MD, PhD,* Michael Mojica, MD*†‡

**Department of Emergency Medicine and †Department of Pediatrics, New York University School of Medicine, New York, NY*
‡Department of Emergency Medicine, Bellevue Hospital Center, New York, NY

Education Gaps

Providers should be up to date on the evidence-based current guidelines for pediatric resuscitation and be able to identify and manage life-threatening illness and injury.

Objectives

After completing this article, readers should be able to:

1. Understand the major changes in the 2015 American Heart Association guidelines for pediatric basic life support, advanced life support, and postresuscitation care.
2. Initiate the management and identify prognostic factors associated with near drowning.
3. Identify the signs and symptoms of life-threatening thoracic injuries, including pneumothorax, hemothorax, flail chest, and cardiac tamponade.
4. Identify and manage cerebral edema in the asphyxiated patient.

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ABBREVIATIONS

AHA	American Heart Association
CPR	cardiopulmonary resuscitation
CT	computed tomography
ED	emergency department
ICP	intracranial pressure
ROSC	return of spontaneous circulation

OVERVIEW

There are common emergencies in pediatrics that any pediatrician needs to be equipped to handle. Common office emergencies include respiratory distress, dehydration, seizures, and anaphylaxis. However, pediatricians also need to be prepared for common conditions that require emergency life support. These include, but are not limited to, cardiac arrest, near drowning, thoracic injuries, and cerebral edema. This article focuses on these common conditions that require emergency life support.

PEDIATRIC RESUSCITATION

Introduction

Cardiac arrest is rare in the pediatric population. In 2015, the American Heart Association (AHA) released updated recommendations for pediatric advanced life support. (1) These updated guidelines, incorporating the available evidence, can guide resuscitation efforts to continue to improve overall survival after pediatric cardiac arrest and, in particular, improve survival with a favorable neurologic outcome.

Basic Life Support

An estimated 6,000 children experience out-of-hospital cardiac arrest per year in the United States. (2) The survival to hospital discharge is 11.3%, and survival with a neurologically favorable outcome is 9.1%. (3) The promotion of bystander cardiopulmonary resuscitation (CPR) remains important. Bystander CPR is performed in out-of-hospital pediatric arrest at an abysmally low rate of 46.5%, with the lowest rates in African American and Hispanic children. (3) Bystander CPR in children increases survival to hospital discharge by 3.7% and increases neurologically favorable outcomes by 2.7%. (4)

The sequence of interventions in cardiopulmonary arrest are different in pediatrics. In 2010, the general AHA guidelines changed from an airway-breathing-circulation (A-B-C) intervention sequence to a circulation-airway-breathing (C-A-B) sequence in an attempt to reduce the time to the first compression. (5) This recommendation was reaffirmed in 2015. However, evidence suggests that the focus on compression-only CPR may not be beneficial in the pediatric population. In infants (<1 year of age), there was no improvement in survival with compression-only CPR compared with no CPR. (3) For older children, the provision of CPR, including rescue breathing and chest compressions, resulted in improved neurologically favorable survival. (3) Given the high rates of asphyxial arrest in the pediatric population, conventional CPR with rescue breathing is recommended. However, starting resuscitation with compressions will not delay the initiation of ventilations by more than 20 seconds. In addition, the sequence of interventions is of less importance in the health-care setting, where more than 1 provider is available and tasks can be accomplished concurrently.

Advanced Life Support

The 2015 updates have been changed to reflect the lack of clear evidence favoring either amiodarone or lidocaine, allowing for the use of either during pediatric cardiac arrest due to ventricular fibrillation and ventricular tachycardia with a pulse. (1) A recent pediatric study demonstrated improvement in the rate of return of spontaneous circulation (ROSC) and 24-hour survival with lidocaine use but no difference in survival to hospital discharge compared with amiodarone use. (6) In 2016, an adult study compared lidocaine with amiodarone and placebo in out-of-hospital cardiac arrest and demonstrated no benefit to either medication over placebo. (7)

There have also been minor modifications to the recommendations for both depth and rate of compressions, with maximums now being added. For depth, the recommendation is that compressions be between 5 and 6 cm due to adult studies showing harm with deeper compressions. (8) There have been no changes to the depth recommendation of 4 cm in infants and 5 cm in children. For rate, the recommendation is now 100 to 120/min based on increased survival with compression rates in that range. (9)

There also continues to be conflicting evidence surrounding the benefits of extracorporeal CPR (extracorporeal membrane oxygenation) in the noncardiac patient. Extracorporeal CPR involves attaching the patient to a machine that externally oxygenates and circulates the blood. There does seem to be clear evidence of improved survival for cardiac patients, both in the postoperative period and otherwise. (10)(11)(12) However, a recent article suggests that it may have general benefits, with the caveat that more patients in the extracorporeal CPR group were patients with a cardiac history. (13)

Postresuscitation Care

Once ROSC is achieved there are evolving recommendations on how to maximize survival to discharge and improve neurologic outcomes. The newest literature focuses on the manipulation of temperature after arrest. There is a clear benefit to avoiding hyperthermia. (14) However, the 2 largest trials on therapeutic hypothermia after in-hospital (15) and out-of-hospital (16) pediatric cardiac arrest did not demonstrate a benefit of hypothermia over therapeutic normothermia.

Hypotension, defined as “a systolic blood pressure less than the fifth percentile for age,” in patients with ROSC should be avoided because it is associated with an increased odds of in-hospital mortality. (17) The recommendations for oxygenation and ventilation goals are less clear. In the pediatric literature, it is uncertain whether hyperoxia (18)(19)(20)(21) or hypercarbia (19)(20) after ROSC have detrimental effects on outcomes. Current recommendations are to avoid extremes and target an oxygen saturation greater than or equal to 94%, but they do not include specific ventilation targets. (1)

The question of when to initiate, or terminate, CPR can be difficult. The AHA defines the goal of resuscitation as “to preserve life; restore health; relieve suffering; limit disability, and respect individuals’ decisions, rights and privacy.” (22) There is currently no single factor or combination of factors that reliably predict outcomes sufficiently to guide recommendations for initiation or termination of CPR. In addition, after ROSC, there are few well-studied factors that reliably predict neurologically favorable outcomes. Given that children's brains have a higher potential for recovery, the decisions surrounding starting and stopping CPR continue to be challenging and should be made in a discussion between the treating physicians and family members. Several studies have shown that it is beneficial to provide families the opportunity to be physically present at the resuscitation because this has been shown to decrease posttraumatic stress disorder–related symptoms (23) and lessen the pain of death (24) without being disruptive to the resuscitative efforts. (25) Early consultation with a palliative care team, even in cases of prognostic uncertainty, can be beneficial because many physicians have difficulty initiating and leading timely discussions on end-of-life care in pediatric patients. (26)(27)

For cardiac arrest in pediatric patients, based on strong research evidence, pediatricians can:

- Continue to encourage conventional CPR with rescue breathing in pediatric patients (3)
- Promote bystander CPR (4)
- Know the role of extracorporeal membrane oxygenation, especially for cardiac patients (10)(11)(12)
- Pay close attention to blood pressure and temperature in the post-ROSC period (16)
- Promote initiatives for the physical presence of families during resuscitation (23)

DROWNING

Introduction

Drowning accounts for 6,000 to 8,000 deaths in the United States (28) and at least 450,000 deaths worldwide annually. (29) Drowning rates are higher in low-income countries and, predictably, in countries with large accessible bodies of water. (30) In the United States, drowning and near drowning commonly occur in homes with pools and near bodies of fresh water. (28) Drowning is more frequent during the summer months and more common in males and non-Hispanic minorities. (31) There is a bimodal distribution in age, with peaks in the toddler and adolescent age groups. (31)

There are multiple individual risk factors for drowning and near drowning. For younger children, the main factor in drowning events is inadequate supervision by adults. (28) Alcohol use is a frequent trigger for these events and is involved in most adolescent drowning events. (28) Overestimating swimming abilities, risk-taking behaviors such as hyperventilating before submerging, and injuries such as cervical spine injuries also contribute to increased drowning rates. (28)

Several studies indicate an increased risk of drowning in children with epilepsy. (32)(33) A meta-analysis of patients with epilepsy demonstrated a 15-fold greater rate of drowning in this population. (32) Adequate anticonvulsant levels may not be protective, and these patients should be specifically counseled regarding water safety.

Apnea and aspiration lead to pulmonary complications and hypoxemia. (34)(35) Systemic hypoxia involves every organ, with poor outcomes attributed primarily to cerebral hypoxia. (36)(37) The primary systems affected are the pulmonary, neurologic, and cardiovascular.

Near Drowning

Near drowning is distinct from drowning in that the victim survives the drowning episode for at least some period. (31) Near drowning rates are uncertain, with an approximate estimate of being 3 to 4 times as common as drowning events. (38) Loss of consciousness is usually included in the definition of near drowning. (28) There are various subcategories of near drowning, including wet near drowning with pulmonary aspiration of fluids as well as dry near drowning with laryngospasm leading to hypoxia without significant aspiration. (39)(40) The clinical importance of these distinctions has not been established. Children who survive drowning may be left with long-term adverse health outcomes, which can increase health-care costs and create difficulty for families. (30)

Prehospital Care

The most important phase of treatment is the prehospital care phase. The most critical factor is immediate resuscitation, including CPR, by witnesses and bystanders. (37) CPR by laypersons has been demonstrated to improve survival. (37) If resuscitation is delayed until emergency medical services arrive, there is a poor chance of survival or survival with good neurologic outcome. (41) Because the main concern in drowning is hypoxia, rescue breathing alone, and compressions if necessary, can improve the rates of morbidity and mortality in near drowning. (37) If supplemental oxygen is available, it should be used to mitigate organ damage due to hypoxia. (37) Rewarming measures should be initiated immediately, especially for a core temperature less than 91.4°F (<33°C). (37) Because these patients have typically swallowed large amounts of water, the high risk of emesis and aspiration can be diminished by placing breathing patients in a lateral decubitus position if CPR is not being performed. (34)

Routine cervical spine immobilization is not recommended for drowning victims without risk factors (such as a shallow dive or signs of trauma) and may actually increase the chances of aspiration. (37) The Heimlich maneuver is not recommended as a method of water expulsion as water in the lungs is rapidly reabsorbed and abdominal compressions increase the risk of regurgitation. (37) Arrhythmias requiring an automated external defibrillator, such as ventricular fibrillation, are rare, and management should not delay CPR. (42)

Emergency Department Care

In the emergency department (ED), early intubation and ventilation, or providing supplemental oxygen as needed, should be considered. (43) The patient should be monitored serially, with cardiac monitoring, end-tidal carbon dioxide monitoring, and oxygen saturation measurements. (34) Patients should be monitored with frequent blood gases and a baseline chest radiograph. (34) Acute respiratory distress syndrome is common; as a result, ventilation with high pressures may be necessary. (44) If there is concern for infection (ie, contaminated water), antibiotics should be administered. (45) An electrocardiogram and serum electrolyte measurements should be performed in near drowning victims, but these rarely show life-threatening or severely abnormal values, although metabolic acidosis is usually present. (46) Euglycemia should be maintained for optimal cerebral perfusion. (37)

Resuscitation and rewarming measures should continue once the patient is brought to the hospital. Multiple passive and active rewarming measures can be used in the ED, including removal of wet clothing, basic drying, protective warmed clothing or blankets, warmed intravenous fluids, inhalation of warmed oxygen, and lavage of body cavities with warmed fluids. (34)(37) Prolonged resuscitative efforts may be necessary in hypothermic patients until core temperatures are increased beyond 91.4°F (33°C). Cases of complete recovery have been observed in hypothermic patients despite cardiac arrest. (47) Therapeutic hypothermia has not proved beneficial, (41) although hyperthermia should be avoided.

Although a variety of ED interventions have been put forth, no specific intervention has demonstrated clear superiority to good medical management alone. Candidate interventions not shown to be clearly beneficial include high-dose barbiturate treatment, intracranial pressure (ICP) monitoring, and protective hypothermia. (42)

Disposition

Hospital admission decisions can be guided by the patient's clinical status. Patients who are initially asymptomatic may develop delayed pulmonary edema as a result of ongoing damage to the alveolar lining. In a retrospective study of 75 pediatric near drowning patients, 98% of patients who had delayed onset of symptoms occurred within 4.5 hours of submersion, and all developed symptoms within 7 hours. (48) Another study confirmed that pediatric near drowning patients could be safely discharged after a 4- to 6-hour observation period if their initial Glasgow Coma Scale score was greater than or equal to 13, they required no advanced life support measures, and they had normal oxygen saturations and pulmonary examination findings after the observation period. (49) A normal chest radiograph in a patient who remains asymptomatic after a period of observation can guide the disposition decision, although chest radiographs were not found to be predictive of the clinical course. (48)

Prognostic Factors

Prognosis mainly depends on prehospital factors. Submersion times play a critical role, with submersions longer than 5 minutes having a poorer prognosis. (50)(51)(52) However, there is no clear submersion timeframe during which a near drowning event has a safer outcome.

Hypothermia is typically thought to result in a better outcome than warm water drowning because hypothermia has been postulated to be neuroprotective, especially if it occurs rapidly. (34)(42)(53) However, this has been questioned in a recent study, with cold water showing no protective effect regarding neurologic outcome. (52)

As mentioned previously herein, early resuscitative efforts are the most important factor in predicting a favorable outcome. (51) Previous studies have demonstrated that resuscitation efforts started within 10 minutes of the drowning episode are more likely to be successful, (51) and resuscitation efforts for longer than 25 minutes are typically associated with poor outcomes. (54)(55) However, there have been some patients with favorable outcomes even with prolonged aggressive resuscitation efforts or prolonged submersion times because neurologic recovery can be difficult to predict in the initial period. (43) In a study of 274 pediatric drowning victims, 17% who continued to be resuscitated after arrival at the ED had functional recovery. (43) This study found 3 predictors of poor clinical outcome: a continuing need for CPR and resuscitative efforts in the ED, a pH less than 7, and coma or apnea in the ED. (43) These results have been supported by other studies. (51) Many prognostic scoring systems have been proposed, but none have been universally accepted.

After 48 hours, if neurologic recovery or improvement is not seen, it would be appropriate to initiate a discussion with the family on possible withdrawal of care. (43) In a study of 44 pediatric patients with near drowning, all of the patients who did not have recovery of spontaneous, purposeful movements within 24 hours had very poor neurologic outcomes or died. (56) In addition, a Glasgow Coma Scale score of less than or equal to 5 and unreactive pupils have been shown to be predictors of poor neurologic outcome. (57)

Prevention

It is hypothesized that 80% of drownings can be prevented. (37) Prevention strategies include appropriate supervision, avoidance of intoxicants such as alcohol, knowledge of swimming and safety, use of appropriate flotation devices during water sports and activities, and the presence of lifeguards. (37)(45) The use of fencing and self-latching gates around pools has been shown to substantially decrease drowning incidents among children. (31)(58) Caregivers should be counseled on appropriate supervision of infants and toddlers in any area of shallow water, including bathtubs. (59)

Infant swimming programs may provide caregivers a false sense of security and should not replace close supervision. In a 2010 policy statement on drowning prevention, the American Academy of Pediatrics reevaluated the age at which swimming lessons can be considered protective based on new evidence. (60) The American Academy of Pediatrics continues to support swimming instruction for children older than 4 years. Several recent studies have suggested that children 1 to 4 years of age may also benefit from lessons, although lessons for this age group are not recommended. (61)(62)

In drowning prevention and near drowning, based on strong research evidence, it is important for pediatricians to:

- Understand the factors that influence prognosis in near drowning (50)(51)(52)
- Provide anticipatory guidance to parents of young children and those with epilepsy regarding water safety (60)

LIFE-THREATENING THORACIC INJURIES

Introduction

Although thoracic trauma occurs infrequently in pediatric patients, it is essential to identify potentially life-threatening injuries to provide prompt medical or surgical interventions. The incidence of thoracic trauma in children has been demonstrated to be between 4% and 8%, with blunt and penetrating trauma accounting for 85% and 15% of cases, respectively. (63)(64) The most common mechanisms of injury in patients sustaining blunt trauma are motor vehicle accidents, intentional injury, and falls. The most common thoracic injuries due to blunt trauma include pulmonary contusions, pneumothorax, hemothorax, and rib fractures. (65) Gunshot wounds, stabbings, and impalement are the most common etiologies of penetrating thoracic trauma resulting in pneumothorax, hemothorax, pulmonary contusion, pulmonary laceration, and blood vessel injury. (65) The mortality rate for thoracic injury is approximately 20%, with a higher rate in penetrating trauma than in blunt trauma. (65)(66) This review focuses on the identification (Table 1) and management (Table 2) of 4 acutely life-threatening thoracic injuries: pneumothorax, hemothorax, flail chest, and cardiac tamponade.

Pneumothorax

Pneumothorax is defined as the accumulation of air in the pleural cavity. Tension pneumothorax occurs when air in the pleural space causes a contralateral shift of the mediastinum (Fig 1). This causes compression of the thoracic vasculature, reducing systemic venous return to the heart and, therefore, reducing cardiac output. Compression of the contralateral lung restricts lung expansion. Children have a higher rate of tension pneumothorax due to greater compliance of the mediastinal structures. Tension pneumothorax is a diagnosis that should be made clinically, and management should not be delayed for radiologic confirmation. Common symptoms include shortness of breath and chest pain. Vital sign abnormalities may include tachypnea, tachycardia, hypotension, and hypoxia. Examination findings may include cyanosis or pallor, contralateral tracheal deviation, ipsilateral decreased breath sounds, and neck vein distention. The absence of lung sliding on a "point of care focused abdominal sonography in trauma" can provide immediate bedside confirmation. Management includes immediate needle decompression in the midclavicular line at the second intercostal space followed by chest tube insertion.

An open pneumothorax, also known as a sucking chest wound, typically results from penetrating trauma. Air preferentially enters during inspiration through the chest wall defect, compromising lung expansion. A sterile dressing that is occlusive on 3 sides (applied when the patient is in full expiration) will prevent air entry through the chest wall defect on inspiration while allowing air to escape from the nonocclusive fourth side during expiration. Definitive management incudes chest tube placement and closure of the chest wall defect.

Hemothorax

Hemothorax is defined as the accumulation of blood in the pleural space. Hemothorax occurs 38% and 64% of the time in pediatric patients with blunt and penetrating thoracic trauma, respectively. (65) A hemothorax is most commonly

TABLE 1. **Life-threatening Thoracic Injuries: Clinical Signs**

SIGN	TENSION PNEUMOTHORAX	MASSIVE HEMOTHORAX	CARDIAC TAMPONADE
Breath sounds	Decreased (ipsilateral)	Decreased (ipsilateral)	Normal
Lung percussion	Hyperresonant (ipilateral)	Dull (ipsilateral)	Normal
Tracheal position	Deviation (contralateral)	Midline	Midline
Neck veins	Distended	Flat	Distended
Heart sounds	Normal	Normal	Muffled

The pulmonary component of the extended focused abdominal sonography in trauma examination can assist in rapidly identifying many of the injuries requiring urgent treatment at the bedside.

caused by penetrating injury through injury to systemic or hilar vessels but may also occur from blunt trauma from rib fractures lacerating the underlying lung or other vascular structures. In the adult-sized patient, a massive hemothorax is defined as more than 1,500 mL of blood in the pleural cavity. In pediatric patients, it is defined as greater than or equal to one-third of a child's blood volume (based on an estimated total blood volume of approximately 80 mL/kg).

Clinical signs and symptoms include tachypnea, hypoxemia, increased work of breathing, ipsilateral absent or decreased breath sounds, tachycardia, and hypotension. Hemothorax can be identified with point of care lung ultrasonography or chest radiography (Fig 2). Blood in the pleural cavity may tamponade bleeding, and, therefore, rapid evacuation may actually cause additional bleeding. For this reason, the patient should be adequately fluid resuscitated before thoracostomy tube placement if time permits. Ongoing bleeding may require packed red blood cell transfusion, activation of a massive transfusion protocol, tranexamic acid, or an operative thoracotomy.

Flail Chest

Flail chest is defined as the fracture of 3 or more consecutive ribs in more than 2 locations. This creates a mechanically unstable floating or flail segment. A review of the National Trauma Data Bank revealed a 1% rate of flail chest in admitted patients at level 1 and 2 trauma centers. (67) In the Israeli National Trauma Registry, 2% and 9% of the documented flail chest injuries occurred in patients aged 0 to 14 years and 15 to 24 years, respectively. (68) The same Israeli study demonstrated a mortality rate of 20%, with the risk of mortality higher with increasing age. (68)

Flail chest is typically due to a blunt mechanism, such as a motor vehicle accident, a vehicle versus pedestrian or bicycle accident, or a fall from a height. It can occur over the anterior, posterior, and lateral thoracic chest wall. The degree of force required to cause a flail chest increases the risk of associated underlying pulmonary injury.

Clinically, external signs of chest trauma are frequent. The unstable floating segment leads to paradoxical chest motion. (69) Normally, contraction of the diaphragm and chest wall expansion outward occurs during inspiration to create the negative intrathoracic pressure required for lung expansion. Paradoxical chest wall motion is observed when the flail chest segment is pulled inward from the negative intrathoracic pressure generated during inspiration. This causes a decrease in lung volumes, atelectasis, chest tightness, and dyspnea. (67)

TABLE 2. **Life-threatening Thoracic Injuries: Emergency Management**

INJURY	TREATMENT
Tension pneumothorax	Needle thoracentesis, tube thoracostomy
Open pneumothorax	3-Sided chest wall dressing, tube thoracostomy
Flail chest	Positive pressure ventilation
Massive hemothorax	Crystalloid/colloid resuscitation, tube thoracostomy
Cardiac tamponade	Pericardiocentesis

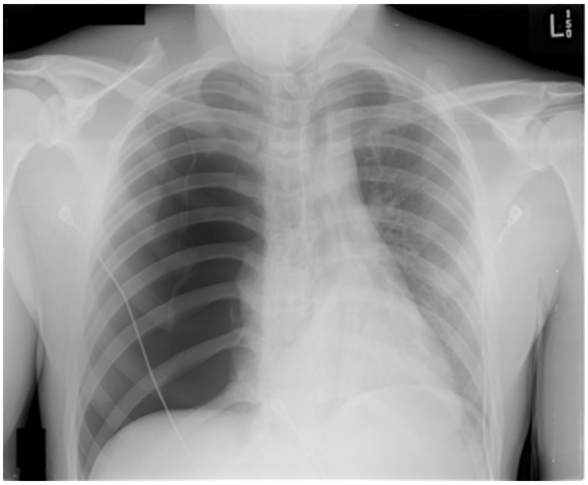

Figure 1. Chest radiograph of tension pneumothorax.

The primary management of flail chest is positive pressure ventilation and possibly surgical fixation. (69)(70)

Cardiac Tamponade

Cardiac tamponade is defined as compression of the heart due to accumulation of fluid in the pericardium; it is potentially life-threatening. (71) The pericardium is an elastic sac with a fixed intrapericardial volume, and once this volume is reached the pericardium loses its elasticity. The accumulation of fluid increases intrapericardial pressure, resulting in decreased systemic venous return, decreased stroke volume, and, subsequently, decreased cardiac output.

Cardiac tamponade can be due to infectious, autoimmune, oncologic, cardiac, metabolic, and traumatic causes. Traumatic cardiac tamponade can be due to blunt or penetrating trauma.

The clinical findings of cardiac tamponade are described by the Beck triad of hypotension, distended neck veins, and distant or muffled heart sounds. Additional findings include tachycardia and pulsus paradoxus. (72) The extent of symptoms is related to the rapidity of fluid accumulation with gradual accumulation having fewer symptoms. Tachycardia compensates to maintain cardiac output in response to decreased stroke volume. Tachycardia may not be present in patients with underlying bradycardia or in patients who present with early tamponade.

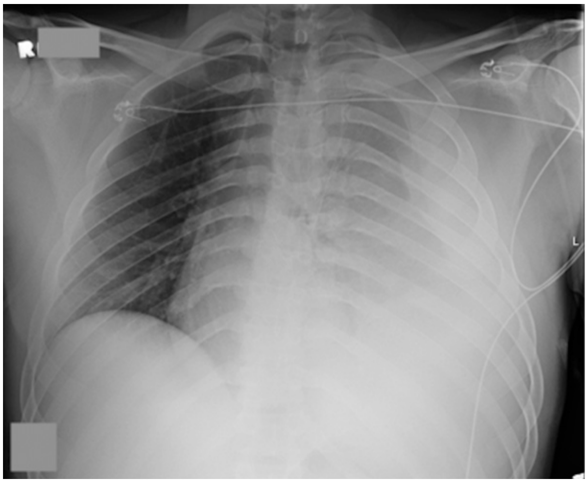

Figure 2. Chest radiograph of massive left hemothorax.

Pulsus paradoxus is defined as "an inspiratory decrease in systolic blood pressure of greater than 10 mm Hg." (72) Pericardial tamponade results in ventricular interdependence, which indicates that the total volume of blood in the heart chambers is constant. An increase in blood volume in one chamber produces a decrease in blood volume in the other chambers. During tamponade physiology, inspiration results in negative intrathoracic pressure. This increases right heart venous return and decreases left heart blood volume, ultimately decreasing systolic blood pressure during inspiration.

Electrocardiography may reveal low voltages, sinus tachycardia, signs of pericarditis such as diffuse ST-segment elevations, or electrical alternans. Low voltage is thought to be due to the pericardial fluid having a dampening effect. Electrical alternans is the alternation of the height of the QRS complex from beat to beat. Electrical alternans is thought to be due to movement of the heart in the pericardial fluid. (71)(72)

Chest radiographs may show an enlarged cardiothymic silhouette. The "point of care focused abdominal sonography in trauma" can directly visualize fluid in the pericardial space and can be used to guide pericardiocentesis.

Management of cardiac tamponade requires removal of the pericardial fluid. This can be accomplished by either pericardiocentesis or surgical drainage. Catheter drainage of pericardial fluid is the preferred method of pericardiocentesis in urgent situations. (72) Surgical drainage with or without a pericardial window is the preferred method for traumatic hemopericardium or purulent pericarditis. (72)

In cases of thoracic injury, it is important for the pediatrician to:

- Use clinical signs and symptoms to rapidly identify life-threatening thoracic injuries (based on some research evidence as well as consensus) (63)
- Understand that point of care ultrasonography, such as the extended focused abdominal sonography in trauma, performed at the bedside can confirm the clinical diagnosis of life-threatening thoracic injury and guide procedures such as pericardiocentesis (based primarily on consensus due to lack of relevant clinical studies)

- Review the rapid interventions that can prevent further deterioration; both supportive care, such as oxygen, ventilation, and fluid resuscitation, and specific interventions, such as needle thoracentesis, tube thoracostomy, and pericardiocentesis, may be required (based on some research evidence as well as consensus) (70)

CEREBRAL EDEMA

Introduction

Cerebral edema is a dreaded and devastating complication of an asphyxial or traumatic event. Asphyxiation can occur by way of several mechanisms in infants and children, including suffocation, choking, and cardiac arrest. Asphyxial cardiac arrest and traumatic brain injury are the most common reasons for children to require some form of cerebral resuscitation. (73) Both asphyxia and traumatic brain injury can result in secondary cerebral injury, including ischemic injury, stimulation of cascades of excitotoxicity, neuronal death, and cerebral edema. (73)

Cerebral edema is defined as excess accumulation of water in the intracellular or extracellular space of the brain. (74) Cerebral edema, if untreated, leads to increased ICP, ischemia, and herniation. Signs and symptoms of cerebral edema in infants and children can be subtle, and early recognition and early intervention are imperative to prevent further neurologic injury and death.

Pathophysiology

The Monro-Kellie hypothesis is that the total volume of the contents of the skull—the brain, cerebrospinal fluid, and blood volume—should be constant at all times. (75) Consequentially, if the volume of one of the contents is increased, the volume of other contents must decrease to compensate. These compensatory mechanisms fail if the volume of brain, blood, or cerebrospinal fluid continues to increase, resulting in a rise in ICP. As ICP rises, cerebral blood flow is decreased, leading to diffuse ischemia and increased cerebral edema with an increased risk for herniation. (74)

After an asphyxia event, edema and increased arterial cerebral blood volume result in cerebral swelling. It is believed that an increase in cerebral blood volume in children may have a greater contribution to cerebral swelling than it does in adults. (76) An open fontanel in infants does not prevent cerebral edema and its complications. (73)

The injury cascade begins with the release of glutamate into the extracellular space, which causes calcium and sodium channels to open. Sodium builds up intracellularly by means of a membrane ATPase pump, thus creating an osmotic gradient for water to flow into the cell. Because of hypoxia, the ATPase pump is eventually inactivated, which reduces calcium and sodium exchange. Because both sodium and calcium increase intracellularly, water continues to move from the extracellular to the intracellular space, and the increase in intracellular calcium stimulates an inflammatory response. This inflammatory response results in the release of free radicals and proteases, which attack cell membranes and blood vessels, causing irreversible cell damage. (75)

Clinical Features

The presentation of cerebral edema varies by both the age of the patient and whether the increase in pressure is acute or chronic. A high index of suspicion is required to quickly identify and treat the underlying process. Failure to act quickly may have devastating consequences.

Symptoms of cerebral edema and subsequent increased ICP include headache, nausea, and vomiting. In nonverbal children and infants, the signs can be subtle and include fussiness, irritability, and somnolence. Papilledema may not be present if the rise in ICP was sudden because it may take days to develop. Occasionally, extraocular movement abnormalities and unequal pupil size are found on physical examination. Less frequently, findings of increased ICP may also include seizures or a preference for the knee-chest position. The Cushing triad is the presence of bradycardia, hypertension, and abnormal respirations. (75) These are late findings and a warning of impending herniation. (75)

Imaging

Neuroimaging should not delay treatment if cerebral edema is suspected. In patients with an acute elevation in ICP secondary to cerebral edema, neuroimaging findings may not be apparent in the first 24 hours. When imaging is obtained, a noncontrast brain computed tomographic (CT) scan is preferred owing to its rapid availability and speed of imaging compared with magnetic resonance imaging. (73) On a CT scan, areas of edema appear as low density, which is caused by the dilution of the components of the white matter. (73) The CT scan can reveal both the presence of edema and the specific type of edema. (75) Magnetic resonance imaging findings on diffusion-weighted imaging windows can show watershed pattern injury with edema.

Nonpharmacologic Management

The assessment of a patient with suspected cerebral edema follows the sequence of airway, breathing, and circulation and the immediate management of conditions identified before assessing neurologic status. If impending respiratory failure, herniation, or loss of airway protection is suspected, the airway should be secured by means of intubation using a cerebroprotective approach to sedation and paralysis. Accumulation of carbon dioxide results in vasodilation of cerebral vasculature and, thus, it is recommended to maintain a Paco_2 of 30 to 35 mm Hg to help prevent the development of intracranial hypertension. (73) A Paco_2 less than 25 mm Hg, an end point that at one time was used to guide ventilator settings, has been found to instead cause cerebral vasoconstriction, leading to worsening hypoxia and cerebral ischemia. (75) Continuous end-tidal carbon dioxide monitoring can be used to assess the degree of hyperventilation.

Elevation of the head of the bed to no more than 15° to 30° allows for venous drainage by gravity. In addition, the patient's head should be kept midline to limit neck vein compression and impaired venous return. (74)

In a patient with cerebral edema, close blood pressure monitoring is imperative. (74) Fluid restriction has a small effect on cerebral edema and, if practiced too aggressively, can lead to hypotension, which may conversely increase ICP. (75) Hypertension can be a compensatory mechanism to maintain cerebral blood flow in the setting of elevated ICP. Rapidly decreasing an elevated blood pressure or failing to address hypotension in a patient with cerebral edema can result in cerebral ischemia and worse neurologic outcomes. (75)

Tight temperature and glucose control in a patient with cerebral edema can have a neuroprotective effect. Previous studies have demonstrated that body temperature higher than 99.5°F (37.5°C) and blood glucose level greater than 150 mg/dL (8.3 mmol/L) are associated with worsening cerebral edema. (75) Therefore, hyperthermia and glucose-containing substances should be avoided in the patient with cerebral edema. Trials of therapeutic hypothermia after in-hospital (15) and out-of-hospital (16) cardiac arrest failed to show a benefit to hypothermia over therapeutic normothermia in pediatric patients.

Pharmacologic Management

Hyperosmolar therapy with 3% hypertonic saline or mannitol is administered to patients with suspected cerebral edema with ICP elevations greater than 20 mm Hg or with clinical signs of impending herniation. (75) The recommended mannitol dose is 0.5 to 1.0 g/kg. This dose can be repeated every 4 hours for sustained ICP greater than 20 mm Hg. Close monitoring of urine output and blood pressure is essential because mannitol promotes diuresis. (75)

Unlike mannitol, hypertonic (3%) saline does not result in diuresis and may maintain hemodynamic stability by maintaining intravascular volume. Hypertonic saline can be administered as an initial bolus of 5 to 10 mL/kg, followed by an infusion of 0.5 to 1.5 mL/kg per hour. (75) Serum sodium levels should be monitored. Serum sodium levels greater than 160 to 165 mEq/L (>160-165 mmol/L) do not provide an additional reduction in ICP. (75)

Additional therapies to consider in patients with raised ICP include antiepileptics and corticosteroids. The role of corticosteroids in head trauma, however, is not well defined. (74)

For patients with cerebral edema, based on some research evidence as well as consensus, it is important for pediatricians to:

- Understand that signs and symptoms of cerebral edema may be subtle in young children and when readily apparent often indicate advanced disease and impending herniation. (73)(74)(75)
- Use both nonpharmacologic methods, such as elevation of the head of the bed, maintenance of normal blood pressure, and control of hyperventilation, and pharmacologic treatment with hyperosmolar therapy, such as mannitol or hypertonic saline, to rapidly reduce cerebral edema if impending herniation is suspected. (73)(74)(75)

References for this article are at http://pedsinreview.aappublications.org/content/40/6/291.

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1. A 9-month-old infant presents to the emergency department after asphyxial cardiac arrest. Which of the following is most likely to increase this child's chances of neurologically favorable survival?
    - A. Bystander cardiopulmonary resuscitation (CPR).
    - B. Compression depth of 2 cm.
    - C. Compression rate of 80/min.
    - D. Use of amiodarone.
    - E. Use of compression-only CPR.
2. Return of spontaneous circulation is achieved in the emergency department in a 2-year-old child who had a witnessed cardiac arrest. Which of the following is currently recommended for postresuscitation care?
    - A. Broad spectrum antibiotics.
    - B. Permissive hypercapnia.
    - C. Target oxygen saturations of 94% or greater.
    - D. 24-hour therapeutic hypotension.
    - E. 24-hour therapeutic hypothermia.
3. A 3-year-old child was found underwater in the family swimming pool in full arrest. Bystander CPR was administered. On arrival at the emergency department, the child is comatose, has a palpable pulse, and is breathing spontaneously, although respirations are labored. Which of the following is the most important next step in the management of this patient?
    - A. Heimlich maneuver to empty the stomach of swallowed water.
    - B. Immediate endotracheal intubation.
    - C. Initiation of broad spectrum antibiotics.
    - D. Maintenance of cervical spine immobilization.
    - E. Measurement of serum electrolytes.
4. A 6-year-old child has hypotension, distended neck veins, and muffled heart sounds after suffering blunt chest trauma in a motor vehicle collision. Breath sounds are equal bilaterally. The nurse notes a pulsus paradoxus of 25 mm Hg. Which of the following is the most appropriate physiologic explanation for the nurse's finding?
    - A. The patient has a flail chest. Outward motion of the flail chest segment during inspiration causes the pulsus paradoxus.
    - B. The patient has an isolated pneumothorax. Hypotension leads directly to the pulsus paradoxus.
    - C. The patient has an isolated pneumothorax. Hypoxia itself causes the pulsus paradoxus.
    - D. The patient has pericardial tamponade. Tachycardia and restriction in ventilation cause the pulsus paradoxus.
    - E. The patient has pericardial tamponade. Ventricular interdependence and increased right heart venous return during inspiration cause the pulsus paradoxus.

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5. A 10-year-old child has had a ventriculoperitoneal shunt in place for several years due to hydrocephalus after surgery for a central nervous system malignancy. The mother notes that the child has been increasingly sleepy during the past 24 hours, has vomited 5 times in the past 8 hours, and complains of a severe headache. On physical examination his heart rate is 50 beats/min and blood pressure is 135/75 mm Hg. He has unequal pupil sizes. His respirations are irregular. On neurologic examination, the child is quite somnolent but does respond slowly to questions. Which of the following is the most appropriate next step in the management of this patient?
    - A. Administer intravenous fluids with a high concentration of glucose.
    - B. Administer labetalol with a target systolic blood pressure of 110 mm Hg.
    - C. Administer mannitol, 0.5 g/kg.
    - D. Administer normal saline, 20 mL/kg.
    - E. Lower the head of the bed.

Common Conditions Requiring Emergency Life Support

Kelsey Fawcett, Nicole Gerber, Shweta Iyer, Guillermo De Angulo, Martin Pusic and Michael Mojica

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Index of Suspicion

1

Progressive Weakness in a Previously Healthy 4-year-old Boy

Kristen Pontiff, MD,* Day Breen, MD,† Pamela McMahon, PhD, MPH,*
Cristina Zeretzke-Bien, MD,‡ Philip Zachariah, MD,§
Christopher Woodward, DO*§

*Pediatric Residency Program, Our Lady of the Lake Regional Medical Center, Baton Rouge, LA
†Neurodevelopmental Disabilities, Pediatric Neurology, Baylor College of Medicine/Texas Children's Hospital, Houston, TX
‡Department of Emergency Medicine, University of Florida, Gainesville, FL
§Emergency Medicine Residency Program–Baton Rouge, Louisiana State University Health Sciences Center, Baton Rouge, LA

EDITOR'S NOTE

Ahh, summertime! Some of us look forward to vacations, perhaps reading on a beach or in a quiet forest. We like summer as we share stories with friends, make new memories, and broaden horizons. Of course, you can take *Pediatrics in Review* along on your summer vacations! You can enjoy the "stories" of *Index of Suspicion* cases, and you can make new memories as you learn of new diagnoses and treatments. You can broaden the scope of your care of future patients. You might even see a patient later this summer who has one of the diagnoses featured in this month's issue. Enjoy!

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A previously healthy 4-year-old boy is carried into the emergency department with progressive weakness affecting all 4 extremities for a 24-hour duration. For the past 2 days, the boy has been more fatigued and complaining of right knee and lower back pain. The parents report no history of trauma. He has a normal appetite, without nausea, vomiting, or recent gastrointestinal illness. He has no dysuria, polyuria or incontinence, chest pain, or cough.

On examination he is afebrile, with normal vital signs. He is mildly distressed, without toxic appearance. There are no obvious rashes, abrasions, ecchymoses, or other findings on exposed skin areas. He is alert and oriented to person, place, and time. On cranial nerve examination his pupils are reactive bilaterally, and extraocular movements are intact. However, slowed smooth pursuit and horizontal nystagmus are observed. Bilateral facial droop is present, along with 4/5 strength of the sternocleidomastoid muscles. He is experiencing diffuse hypotonia, with no spontaneous movement of the bilateral lower extremities. He has 2/5 strength in the distal upper extremities bilaterally. Deep tendon reflexes are absent. He has intact sensorium throughout. Examination of the joints reveals

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normal passive range of motion. All other physical examination findings are normal.

DISCUSSION

After a thorough examination of the skin, an engorged tick was detected on the scalp and was properly and fully removed. Findings on laboratory evaluation were normal, including a complete blood cell count, C-reactive protein level, complete metabolic panel, and erythrocyte sedimentation rate. The boy was admitted to the hospital. Within 8 hours of tick removal he was sitting unsupported, and by 12 hours he was ambulating without assistance.

Differential Diagnosis

Acute-onset paralysis in children has a broad differential diagnosis, and it is important to establish whether the paralysis is due to an upper motor neuron versus a lower motor neuron lesion. Given the boy's neurologic examination findings, with absent reflexes, the paralysis is likely due to a condition affecting lower motor neurons. Some conditions to be considered are Guillain-Barre syndrome and transverse myelitis. One can distinguish among these conditions by performing an adequate neurologic examination.

Guillain-Barre syndrome, in particular, affects the peripheral nerves by demyelination. The classic presentation is a viral illness with an upper respiratory tract infection or gastrointestinal illness 1 to 2 weeks earlier, followed by a symmetrical ascending motor weakness. Lower extremities are affected more than upper extremities. Areflexia and paresthesia are also present.

Transverse myelitis is a neurologic condition that presents at a distinct motor or sensory level. Most patients presenting with transverse myelitis will have physical examination findings that point to a specific area of the spinal cord. This helps to differentiate Guillain-Barre syndrome and tick paralysis, which affects the nervous system more globally.

The Condition

Tick paralysis is caused by 2 major tick vectors in the United States: the dog tick and the wood tick. The female tick attaches onto its host and injects a neurotoxin that is believed to block acetylcholine release. In the United States, children and girls are more frequently affected than adults and boys, respectively. It is thought that girls are disproportionately affected because the tick remains unnoticed on the scalp due to their long hair. Its incidence is highest during mating season (February to August). Mortality of those affected by tick paralysis ranges from 6% to 13%. Seventy-nine percent of these deaths occur in children younger than 16 years. Respiratory failure is the primary cause of mortality because of failure to recognize that the paralysis was caused by the tick bite and, therefore, delay in removal of the tick to prevent respiratory muscle paralysis.

Most affected children have nonspecific symptoms, including a 4- to 7-day prodrome of restlessness and irritability, followed by ascending paralysis. Bulbar lesions can be apparent on physical examination and may cause dysphagia and slurred speech. Local skin reactions have also been noted and are described as morbilliform rash. These rashes are different than the centripetal rash seen with Rocky Mountain spotted fever. Although symptoms of many parasite infections continue long after tick removal, tick paralysis symptoms resolve rapidly after removal of the tick.

Diagnosis

Characteristic signs and symptoms coupled with response to removal of the offending tick are enough to establish the diagnosis, and further evaluation is not necessary.

Management

Removal of the tick is the most important aspect of tick paralysis. Proper removal of the tick, including the head, which is usually lodged under the skin, will result in complete resolution of symptoms over a 24- to 48-hour period. A few case studies have reported weakness lasting up to 1 week.

To achieve proper removal of the engorged female tick, one must grasp the tick at the base of the head and remove. This can be accomplished with special tweezers that do not put pressure on the body of the tick. The most safe and efficient way to remove the tick is with tick keys, which slide over the body and, when pulled slowly sideways, removes the entire tick.

Education on how to properly remove ticks is vital, especially for those who live in areas where tickborne illnesses are prevalent. It is imperative to relay that burning and use of petroleum jelly products, 2 commonly used methods, are ineffective in tick removal. In addition, it has been reported that practitioners who removed ticks without gloves have developed transient paralysis.

Progression to respiratory compromise and failure will occur without removal of the offending tick. Patients who experience respiratory failure may need aggressive intervention, including intubation and ventilator support until the toxin effects subside.

To date, there is no evidence of other tickborne illnesses in patients with tick paralysis, and for this reason additional evaluation for tickborne illnesses is not recommended.

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Lessons for the Clinician

- Tick paralysis is a relatively rare but easily diagnosed condition in children with acute-onset ascending paralysis.
- Children presenting with ascending paralysis should be carefully examined from head to toe, with care taken to fully examine hair-bearing areas, areas between toes, and in and around the ears.
- Signs of lower motor neuron paralysis, intact sensation, and resolution of paralysis on removal of the tick establish the diagnosis of tick paralysis.
- Proper removal of the tick is the mainstay of treatment.

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Case 1: Progressive Weakness in a Previously Healthy 4-year-old Boy

Kristen Pontiff, Day Breen, Pamela McMahon, Cristina Zeretzke-Bien, Philip Zachariah and Christopher Woodward

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Index of Suspicion

2 16-year-old Boy with Intractable Nausea and Vomiting

Emily Kelly, MS,* Elizabeth Van Opstal, MD†

*Rush Medical College, Chicago, IL

†Rush University Medical Center, Chicago, IL

PRESENTATION

A 16-year-old boy with a medical history of mild intermittent asthma presents to the emergency department with a 4-day history of achy, 8/10 epigastric and periumbilical abdominal pain with intractable nonbilious, nonbloody emesis. He has presented with similar episodes 3 times previously at another hospital, without a definitive diagnosis being made. He also has new-onset chest pain (6/10) since the morning of presentation that radiates to his back. This pain is associated with neck swelling and "air pockets" under the skin. He states that such air pockets have occurred previously with episodes of prolonged emesis. He denies diarrhea and has been afebrile. He states that hot showers improve his abdominal pain and emesis; he often showers up to 10 times a day. He has been taking omeprazole for presumed gastritis diagnosed 1.5 months ago at an outside hospital, but he takes no other medications. He acknowledges a history of frequent marijuana use.

Vital signs are significant only for a heart rate of 114 beats/min. He appears to be in mild distress. Findings from cardiovascular and respiratory examinations are normal other than tachycardia. Scleral icterus and mild jaundice are noted. Marked, diffuse subcutaneous emphysema is palpated from his anterior chest to right neck and lateral face. The abdomen is soft, nontender, and nondistended, with normoactive bowel sounds and no appreciable masses. His neurologic examination findings are normal, including strength, sensation, and reflexes of the upper and lower extremities. Laboratory results are remarkable for an elevated white blood cell count (14,500/μL [14.5×10^9/L]), hyponatremia (sodium level, 129 mEq/L [129 mmol/L]), and hypochloremia (chloride level, 91 mEq/L [91 mmol/L]). Lipase, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels are normal. A chest radiograph is obtained (Fig 1).

DISCUSSION AND DIAGNOSIS

Kidney, ureter, and bladder radiography is ordered to rule out free air associated with the patient's abdominal pain and emesis. It displays a normal bowel gas pattern. The persistent nausea and vomiting are thought most likely to be due to cannabinoid hyperemesis syndrome (CHS); this is supported by his history of

AUTHOR DISCLOSURE Ms Kelly and Dr Van Opstal have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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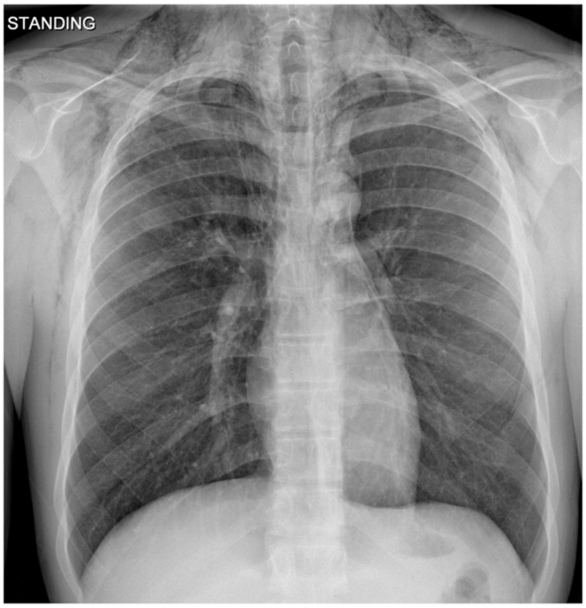

Figure 1. A chest radiograph the day of admission demonstrates subcutaneous emphysema.

relief from hot showers. He undergoes subsequent upper endoscopy, which shows only mild gastritis.

A chest radiograph confirms the presence of extensive subcutaneous emphysema, as well as possible pneumomediastinum. No evidence of a pneumothorax is found. A computed tomography angiogram of the chest confirms extensive subcutaneous emphysema, as well as pneumomediastinum and pneumorrhachis (Fig 2). Pediatric surgery is concerned for esophageal perforation as the etiology for the subcutaneous emphysema, so they recommend an esophagogram. It is negative for esophageal leak or perforation. The pneumomediastinum is thought to be a spontaneous result of excessive emesis. Neurosurgery is consulted for his pneumorrhachis. Computed tomography of the spine shows extensive involvement; however, neurologic examination is normal, and the patient is completely asymptomatic.

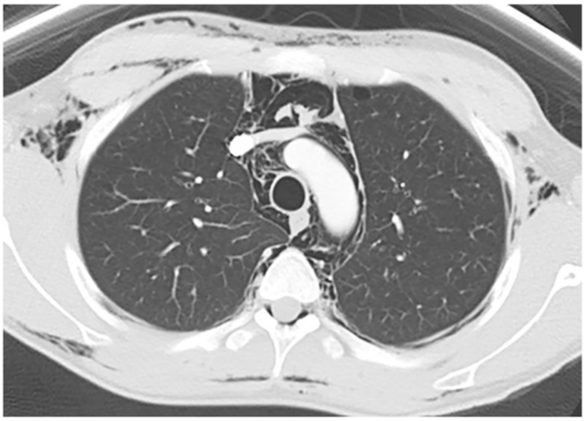

Figure 2. A computed tomographic scan of the chest with intravenous contrast on the day of admission demonstrates extensive subcutaneous emphysema, pneumomediastinum, and pneumorrhachis.

Case reports and presentations of CHS are well documented in the adult literature. However, because it is a clinical diagnosis without laboratory or radiographic screening tests, misdiagnosis is common. (1) Typically, patients present with abdominal pain, nausea, and recurrent emesis in the context of a significant history of cannabis use. The syndrome is commonly described as having 3 distinct phases. During the prodromal phase, which, if present, lasts anywhere from a few months to a few years, the patient experiences early-morning nausea and a fear of vomiting, but maintains a normal appetite and may continue or increase cannabis use. The hyperemetic phase follows and involves intense, cyclic vomiting episodes lasting 24 hours to several days. The patient will classically relieve these episodes with hot showers. This phase of the syndrome is typically when patients report to the emergency department for rehydration; evaluation is usually normal. The final recovery phase begins only once the patient ceases cannabis consumption. Relief usually occurs within a week. (1)(2)

The definitive treatment of CHS is cessation of cannabis use. During the hyperemesis phase, rehydration with intravenous fluids and supportive care are the cornerstones of management. Dehydration due to intractable vomiting and frequent, prolonged hot showers is common in patients with CHS; case reports of acute kidney injury in adults with CHS reinforce how important rehydration with kidney function monitoring is during treatment of CHS. (3) Standard antiemetic agents, such as ondansetron, generally do not provide symptomatic relief of nausea and vomiting. (1) Some preliminary case reports regarding the effectiveness of topical capsaicin cream at relieving abdominal pain and vomiting in both adult and pediatric populations with CHS are promising. (4) Counseling on cannabis cessation with outpatient follow-up is suggested to prevent recurrence of CHS.

Although spontaneous pneumomediastinum (Hamman syndrome) is a well-documented adverse effect of intractable vomiting, the literature does not specifically cite CHS as a precipitating etiology. Other commonly cited causes of pneumomediastinum include coughing, Valsalva maneuver, bronchial asthma, and deep sea diving. (5) In this condition, alveoli become overdistended to the point of rupture, releasing free air that diffuses to the mediastinum. (5)(6) Incidence overall in pediatric populations is 1 in 8,000 to 1 in 15,000. (7) Clinically, pneumomediastinum

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in children most commonly presents as chest or neck pain, but it can also include sore throat, cough, dyspnea, or pain that radiates to the back. Chest radiography is diagnostic in most cases, and follow-up can usually be performed clinically, without the need for further studies. (7) A 2016 retrospective study revealed that all esophagrams performed in the setting of spontaneous pneumomediastinum to evaluate for the presence of esophageal rupture were negative, and, therefore, some experts do not think that they are indicated. (8) Treatment is mostly supportive and must address the underlying cause of the pneumomediastinum. (7)(9)

Pneumorrhachis, in which air from ruptured alveoli enters the spinal cord at either the epidural or subdural level, is an extremely rare condition, especially as a complication of pneumomediastinum. Documented cases indicate that spinal trauma and epidural placement are the most common cause of spontaneous, isolated, pneumorrhachis, although violent vomiting, abscesses, asthma, and coughing can precipitate this condition. (5)(10) In the case of pneumorrhachis after pneumomediastinum, free air from the mediastinum travels to the fascia of the neck, at which point it crosses the neural foramen to the epidural space. (5) Computed tomography of the spine is the most reliable diagnostic tool. In most cases, patients are asymptomatic, although neurologic deficits have been documented in a few cases, and meningitis is a rare possible adverse effect. (6)(10) Conservative management for asymptomatic patients is supportive, with attention given to any underlying conditions. Needle decompression, dexamethasone, and hyperbaric oxygen treatment are nonsurgical treatment options previously documented for use in refractory or symptomatic cases. (10)(11)

Our patient, unfortunately, did not quit using marijuana and had frequent subsequent emergency department visits and hospitalizations. He did not have further incidents of pneumomediastinum or pneumorrhachis.

Adolescents' access to marijuana continues to increase as more states legalize its use, necessitating that clinicians screen for use during routine health maintenance intakes and keep a high index of suspicion for CHS among those who present with cyclic vomiting (4).

Lessons for the Clinician

- In pediatric patients with intractable nausea and vomiting without relief from classic therapies, maintain a high index of suspicion for cannabis hyperemesis syndrome, especially in those who endorse a history of marijuana use.
- Although emerging studies suggest that topical capsaicin cream may help relieve nausea and vomiting in patients with CHS, the only definitive treatment is cessation of marijuana use.

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Case 2: 16-year-old Boy with Intractable Nausea and Vomiting

Emily Kelly and Elizabeth Van Opstal

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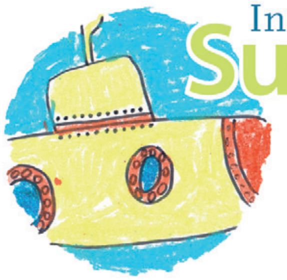

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3 Prognathism in a 13-year-old Boy

Jacqueline T. Chan, MD,* Carla Z. Minutti, MD†

*Children's Hospital University of Illinois at Chicago, Chicago, IL
†Rush University Medical Center, Chicago, IL

PRESENTATION

A previously healthy 13-year-old boy presents to the clinic for evaluation of prognathism. The mother reports that his jaw has grown disproportionately in the past 2 years and he is unable to close his mouth. The mother also mentions that he has been growing fast for the past 3 to 4 years and that she has frequently been buying him larger shoes and clothes. He denies headaches or blurry vision. Family history is negative for prognathism or tall stature. On examination he is found to be above the 95th percentile for height (midparental height around the 20th percentile), and his weight is at the 90th percentile. His vital signs are normal. Physical examination is pertinent only for prognathism. He is unable to completely close his mouth. He is Tanner stage 4-5.

Review of previous records shows crossing of height percentiles from the 75th to above the 95th from 9 to 11 years old, whereas his weight has been stable. Records before this age were not available because the patient is an immigrant. A bone age is read as 17 years at a chronological age of 13 years.

Hormonal evaluation reveals a growth hormone (GH) level of 7.3 ng/mL (7.3 μg/L) (reference range, <5.0 ng/mL [<5.0 μg/L]) and an insulinlike growth factor 1 (IGF-1) level of 725 ng/mL (95 nmol/L) (reference range, 90–589 ng/mL [12–77 nmol/L]), which are borderline high for his pubertal stage. Luteinizing hormone, follicle-stimulating hormone, and testosterone levels are late pubertal. Other pituitary hormone levels are normal. Other tests and imaging (Fig) reveal the diagnosis.

DISCUSSION

Described is a 13-year-old boy with prognathism presenting to the pediatric endocrinology clinic, being referred by his dentist. Growth chart review revealed abnormal growth velocity starting at age 9 years. On presentation, other possible etiologies for abnormal growth velocity were evaluated, including precocious puberty and hyperthyroidism. For males, precocious puberty is defined as the onset of puberty before age 9 years. Our patient may have also had a component of earlier puberty, which may have contributed to the fast growth and earlier closure of epiphysis. Hyperthyroidism was ruled out with normal thyroid function test results. Neither early puberty nor hyperthyroidism present with prognathism. He did not have any other facial dysmorphic features or neurocognitive problems to suspect any syndromic or chromosomal cause of tall stature, including Soto, Klinefelter, or XYY syndrome. There were no skin findings to support a diagnosis of neurofibromatosis or McCune-Albright syndrome.

AUTHOR DISCLOSURE Drs Chan and Minutti have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Chan's current affiliation is Medical College of Georgia at Augusta University, Augusta, GA.

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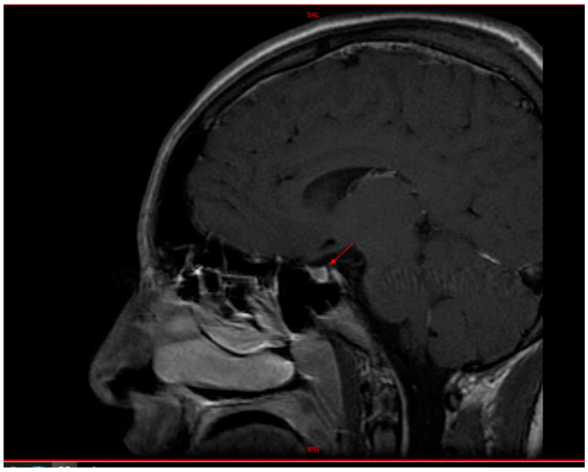

Figure. Magnetic resonance image showing pituitary adenoma.

Laboratory tests showed GH levels above limits of normal, IGF-1 levels were borderline high for pubertal status, and a GH suppression test was abnormal (GH level after oral glucose load of 1.12 ng/mL [1.12 μg/L], normal is <0.3 ng/mL [<0.3 μg/L]). The clinical picture, in conjunction with the test results, suggests a diagnosis of gigantism. Magnetic resonance imaging with contrast reveals a pituitary adenoma. No other testing was performed for the diagnosis of early puberty after finding the pituitary adenoma.

His Tanner stage and pubertal hormones were compatible with a postpubertal stage at age 13 years, so he may have had a component of early puberty, also caused by his pituitary adenoma. This may have contributed to the advancement of his bone age.

Pituitary gigantism results from persistent increased secretion of GH. This excess will stimulate the secretion of IGF-1, causing clinical manifestations. Patients with excess GH secretion before fusion of growth plates will present with increased growth velocity with concurrent rapid weight gain, growth of hands and feet, frontal bossing, and macrognathia. Research by Rostomyan et al on an international collaborative study of 208 patients shows that the most frequent initial clinical sign is increased growth velocity, which is observed in 75% of patients. This is followed by acral enlargement in 37% of patients. Acromegaly is due to excessive GH production after epiphyseal closure. Manifestations of acromegaly include increased skull circumference, broadening of the nose, enlargement of the tongue, coarsening of the facial features, excessive mandibular growth causing prognathism, separation of the teeth, thickening of the fingers and toes, and dorsal kyphosis. The average time of presentation is late prepubertal childhood or early adolescence, with a median age of 13 years. The GH and IGF-1 levels are clues for diagnosis, but a normal test does not rule out the condition. A glucose suppression test should be performed to confirm excess GH production. Ingestion of 1.75 g/kg of glucose (maximum of 75 g) causes insulin secretion, leading to suppression of IGF binding protein 1. This causes an acute increase in free IGF-1 levels. The increased free IGF-1 suppresses GH secretion within 30 to 90 minutes. A GH nadir of less than or equal to 0.3 to 1.0 ng/mL (≤0.3–1.0 μg/L) is considered normal. Confirmation of this diagnosis warrants imaging to evaluate for the presence of an intracranial mass. Depending on the size of the pituitary mass, headaches and visual changes can also be present. Overproduction of GH can be an isolated abnormality or part of a syndrome, including McCune-Albright syndrome and multiple endocrine neoplasia type 1. History and physical examination is very important. Surgical removal of the tumor is the treatment of choice but is not always curative. Physical changes such as bone enlargement that occur due to excess GH are irreversible and require surgical correction. Surgery should be postponed until GH and IGF-1 levels normalize.

After transsphenoidal resection of the pituitary adenoma, the patient was followed to rule out recurrence of pituitary adenoma or hypopituitarism. On follow-up, no further mandible growth was reported, and all laboratory evaluations were normal. Repeated magnetic resonance imaging showed no evidence of a pituitary mass. He was then referred for jaw reconstruction.

Lessons for the Clinician

- Clinical presentation of children with pituitary gigantism varies.
- Children who present with increased growth velocity and acral enlargement or broadening of facial features warrant investigation of growth hormone excess.

NOTE. This case is based on a presentation by Dr Carla Minutti at the European Society for Paediatric Endocrinology yearly meeting in Paris, France, on September 10–12, 2016. Poster session: Syndromes: Mechanisms and Management; Poster number: P2-877; Session date: September 12, 2016; Session time: 13:45–14:45 PM. Portions of this case have been previously published as part of the aforementioned conference presentation.

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Case 3: Prognathism in a 13-year-old Boy

Jacqueline T. Chan and Carla Z. Minutti

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4 Delayed Passage of Meconium, Abdominal Distention, and Emesis in a 2-day-old Girl

Leslie Mataya, MD,* Poj Lysouvakon, MD*

*Department of Pediatrics, University of Chicago Medical Center, Chicago, IL

PRESENTATION

A full-term newborn is delivered via normal spontaneous vaginal delivery to a 38-year-old gravida 5, now para 5005 mother. The mother underwent elective induction of labor for preeclampsia without severe features. The mother received adequate prenatal care, and serologic tests were negative apart from group B *Streptococcus* colonization, for which she received adequate intrapartum antibiotic prophylaxis. The labor and delivery course was uneventful, and Apgar scores were 9 and 9 at 1 and 5 minutes, respectively, with suction, drying, and stimulation. Birthweight was 3,270 g (appropriate for gestational age); length, 52 cm; and head circumference, 33 cm. For the first 24 hours after delivery, the infant took the bottle well, with minimal regurgitation. The abdomen was soft and nondistended. Now, on postnatal day 2, her intake by mouth is decreased, her abdomen has become firm and distended, and she is having more large-volume emesis that is nonbloody and nonbilious. She has also failed to pass meconium for more than 24 hours. Abdominal radiographs are obtained that show multiple dilated loops of bowel with absence of distal air, consistent with a distal bowel obstruction (Fig 1). An urgent surgical consult is requested and a nasogastric tube is placed, the output of which becomes frankly bilious over the next few hours. Of note, the infant has a half-sister with a history of Hirschsprung disease requiring diverting loop ileostomy.

DISCUSSION

Differential Diagnosis of Delayed Passage of Meconium

This differential diagnosis includes colonic aganglionosis (Hirschsprung disease), intestinal atresia/webs, malrotation with or without volvulus, anorectal malformations, meconium ileus (usually secondary to cystic fibrosis), meconium plug syndrome, small left colon, drugs during delivery (magnesium sulfate, opiates, or ganglionic blocking agents), or hypothyroidism. Another cause could be functional ileus, which occurs in the setting of prematurity, sepsis, respiratory distress, pneumonia, or electrolyte disturbances.

Delayed passage of meconium itself, without other concerning symptoms, does not necessarily warrant urgent surgical consultation. However, particularly in light of the bilious output that emerged after nasogastric tube placement in this case, some of the more serious anatomical malformations included in our differential diagnosis should be considered. These do require immediate

AUTHOR DISCLOSURE Drs Mataya and Lysouvakon have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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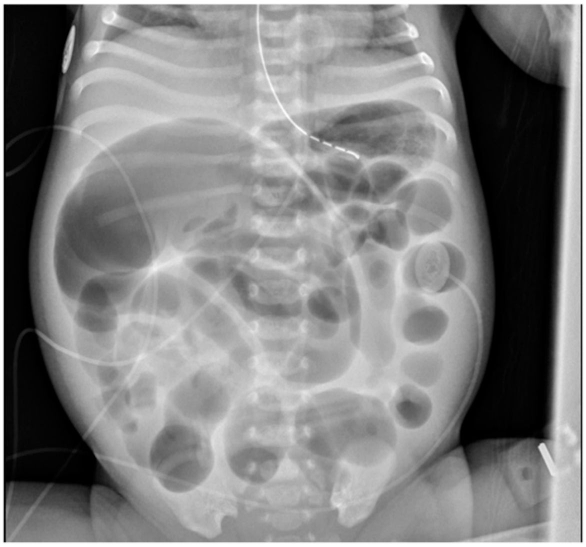

Figure 1. Abdominal radiograph showing distended, tubularlike bowel loops with absence of distal air.

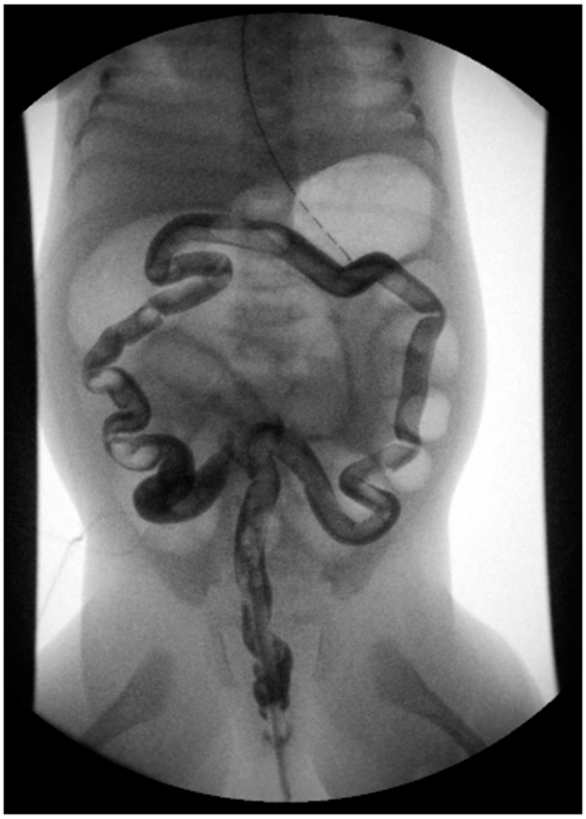

Figure 2. Contrast enema radiograph showing total microcolon on a background of distended small-bowel loops.

surgical consultation and intervention to avoid gut perforation or compromised gut viability. The urgent or "stat" timing of this consultation is particularly important if abdominal radiographs are abnormal (ie, show a pattern of intestinal obstruction or perforation). In fact, some pediatric surgeons have argued that any term baby with bilious vomiting should undergo an upper gastrointestinal contrast study to definitively exclude malrotation, given the serious nature of this problem and its potentially devastating sequelae.

Given this infant's family history of Hirschsprung disease, delayed passage of meconium for more than 24 hours, as well as the abdominal radiographs concerning for distal bowel obstruction, a lower gastrointestinal contrast study was obtained. This showed total microcolon on a background of distended small-bowel loops concerning for distal small-bowel atresia or total colonic aganglionosis, also known as Hirschsprung disease (Fig 2). This narrowed the differential diagnosis significantly, and she was taken to the operating room late on postnatal day 2 for definitive diagnosis of total colonic with small-bowel aganglionosis (involvement up to 80 cm proximal to the ileocecal valve).

The Condition

Hirschsprung disease consists of a collection of conditions that have aganglionosis of the intermyenteric plexus as a common feature. It is classified into ultra-short–, short-, and long segment disease. Long-segment disease is further classified into colonic, total colonic, and total colonic with small-bowel aganglionosis. Total colonic aganglionosis is an uncommon form of Hirschsprung disease, affecting 2% to 13% of Hirschsprung cases. Affected families can carry a 200 times higher risk of recurrence. The initial presentation of long-segment disease is often functional obstruction at or shortly after birth, although a later presentation is not uncommon. Radiologic diagnosis, particularly in newborns, is difficult because findings are not consistent. However, there are distinct patterns seen with contrast enema that are being identified with an increased likelihood of total colonic aganglionosis: microcolon and question mark–shaped colon. Hirschsprung disease is generally thought to be a genetic, sex-modified, multifactorial condition with variable severity and incomplete penetrance. Total colonic aganglionosis, however, may have a different signaling pathway because it is much more common in familial series, and length of involvement increases with successive generations (suggesting a possible autosomal dominant inheritance pattern with increased gene penetrance in successive generations). The *RET* and *EDNRB* genes are the 2 major susceptibility pathways for Hirschsprung disease and total colonic aganglionosis.

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Complications, Treatment, and Outcomes

Either before surgery or in the immediate postoperative period, Hirschsprung-associated enterocolitis is a major life-threatening complication that can affect up to half of these patients. This can present as abdominal distention, explosive diarrhea, emesis, fever, lethargy, and even shock. Surgical management of total colonic aganglionosis via a variety of techniques has been shown to be successful. However, results are suboptimal, sequelae are very common, and mortality is relatively high (∼15%), particularly in those with extensive small-bowel involvement. Patients with this condition often undergo multiple complications and reoperations. In general, patients start with a stoma and are eventually reconnected to allow voluntary bowel movements. Approximately half of the patients achieve good bowel control long term, and the other half have problems maintaining continence. They will start with an average of 5.2 bowel movements per day, decreasing to 3.4 at age 15 years. Iron deficiency anemia and growth delay are also common sequelae in these patients.

Lessons for the Clinician

- Most full-term neonates will pass meconium in the first 24 hours of postnatal life. Failure to pass meconium after 48 hours, or sooner if other concerning symptoms are present, would warrant an investigation as to the cause of the delayed passage of meconium.
- Urgent or "stat" surgical consultation is of the utmost importance in cases of delayed passage of meconium that are accompanied by other concerning symptoms, such as bilious emesis or a firm and distended abdomen.
- Hirschsprung disease, including total colonic aganglionosis, is a rare yet clinically significant cause of delayed passage of meconium, abdominal distention, and feeding intolerance in the neonatal period.

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Case 4: Delayed Passage of Meconium, Abdominal Distention, and Emesis in a 2-day-old Girl

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Vulnerable Child Syndrome

Kristine Schmitz, MD*
**St Christopher's Hospital for Children/Drexel University College of Medicine, Philadelphia, PA*

Vulnerable child syndrome (VCS) describes a phenomenon in which a child is perceived as being at higher risk for medical, behavioral, or developmental problems than is warranted by the child's current health. It is most often thought to occur in children who have experienced a serious or life-threatening event or who have a chronic medical condition. However, VCS should be considered a maladaptive family dynamic and can also occur in families that have not experienced a significant event, particularly where parental mental health needs are unmet. Parental perception of exaggerated risk may lead to overuse of medical services, possible unnecessary interventions, and poor parenting practices, parent-child attachment, and child development.

Several factors may predispose families to develop these maladaptive relationships and perceptions of their child. Infertility, pregnancy loss or emergent pregnancy complications, and premature birth may result in VCS. While the child is in the NICU, parents of premature infants face uncertainty about their child's health, and many premature children develop chronic medical problems, many of which require subspecialty involvement. In addition, parents of children who have experienced a life-threatening event (eg, intubation due to respiratory syncytial virus) or diagnosis (eg, cancer) may continue to fear serious illness even after the illness has resolved. Similarly, children diagnosed as having chronic medical conditions, such as asthma or type 1 diabetes, require ongoing management and can have exacerbations, increasing the risk of parental misperception of vulnerability. Last, early childhood feeding difficulty or excessive crying may predispose families to develop VCS.

Parental mental health is an important consideration in identifying risk factors for the development of VCS. Acute stress disorder or posttraumatic stress disorder in parents of children who have received intensive care or who had a life-threatening event is well described. In addition, parents who have unmet mental health needs, particularly depression, somatization, anxiety, obsessive-compulsive disorder, and trauma exposure, along with social stressors, may be at higher risk for the development of VCS. If a parent copes poorly with the initial traumatic event and lacks social support, he or she may be at higher risk for exaggerated beliefs about the child's vulnerability. Increasingly, pediatricians are more prone to routinely screening for mental health and social concerns among parents, and it is critical to consider these concerns when evaluating the family.

When a parent erroneously views the child as more vulnerable than she or he is, the parent-child relationship is negatively affected. It can result in impaired parenting, including poor limit setting, overindulgence, or inappropriate attachment, and can affect the child's cognitive and behavioral development. Children may miss excessive school days or other important educational and sociodevelopmental opportunities. The child may also subconsciously develop the symptoms that the parent is worried about, reinforcing the parent's

AUTHOR DISCLOSURE Dr Schmitz has no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Consultation of the Specialist: The Vulnerable Child Syndrome. Pearson SR, Boyce WT. *Pediatr Rev.* 2004;25(10);345–349

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A Model for the Development of Mothers' Perceived Vulnerability of Preterm Infants. Horwitz SM, Storfer-Isser A, Kerker BD, et al. *J Dev Behav Pediatr.* 2015;36(5):371–380 misperception. Children may experience increased anxiety, somatization, social phobia, school refusal, or impaired social interactions in these circumstances. They also may overestimate their own medical risk.

Also, VCS may impair the parent-provider relationship. Parents may feel that their concerns are not being heard or taken seriously. This may lead to "doctor shopping," difficulty maintaining engagement in the pediatric medical home and with the primary care provider, and excessive use of emergency departments.

The pediatrician's approach to families experiencing VCS should be trauma-informed and empathetic, while working to challenge erroneous beliefs in the setting of a safe and trusting relationship. Ideally, this approach would be multidisciplinary and coordinated by the child's medical home so that the family receives consistent messaging and support. The pediatrician should first acknowledge and validate the family's past experiences, as well as fears of a current or future medical problem. In many cases, their child may be at risk for exacerbations or medical crises in the future and may develop behavioral or physical concerns that warrant intervention. At the same time, it is critical to provide clear communication about the current risk or lack thereof and to neutrally address the anteceding event. Ultimately, the goal is to develop a trusting partnership in which the parent feels respected so that honest communication and belief challenging can take place.

Mental health screening for depression and anxiety coupled with gently discussing the association of these symptoms with increased perceived vulnerability may help identify supports for a family. Therapy to address preexisting mental health conditions and distress caused by the child's medical history can be tremendously helpful. For example, there is robust evidence that trauma-focused cognitive behavioral therapy (TF CBT) assists parents of premature infants in reducing stress, anxiety, posttraumatic stress disorder, and depression. It is less clear whether TF CBT specifically reduces the perception of child vulnerability owing to lack of research. In 1 study of mothers of premature infants, Horwitz compared 6 to 9 sessions of TF CBT with standard education and peer support. Parental perception of child vulnerability was reduced in both groups, with a slightly higher reduction among the mothers who received the TF CBT intervention. This finding suggests that connecting parents with some form of support services, including TF CBT, psychoeducation, or peer mentors, with a focus on restructuring beliefs about their child's vulnerability may be useful. Further research to investigate generalizability is needed to further define best practices for helping parents experiencing this phenomenon. It is also important that pediatricians take care to sensitively address parental mental health concerns and anticipate that parents may be defensive. It may take a strong relationship with the pediatrician and numerous discussions before parents are willing to engage in therapy.

The pediatrician should challenge exaggerated beliefs even if the family is not engaged in therapy. Cognitive reframing is best performed after a strong rapport is built and in conjunction with providing practical tools that parents can use when their anxiety rises. These tools might include "if this, then" planning, wherein an action plan for common parental concerns is developed, including education about home management techniques, and access to an on-call provider for questions or concerns. It is important that families and providers continue to communicate and reassess because the health status may change and parental willingness to try new approaches, or new fears may emerge. In rare cases, medical abuse may occur with VCS, and pediatricians must be aware of this possibility and refer to child protective services when appropriate.

Parental perception of child vulnerability or VCS is an important phenomenon that may occur in children who have experienced serious medical concerns and in children who are healthy but whose parents face psychosocial stressors. Recognizing it and knowing how to address it with families is critical to prevent negative child outcomes. It is best addressed with an empathetic approach, ongoing monitoring, and relationship building, along with integrated mental health and social support services.

COMMENT: Understanding the concept of the VCS is critically important in our profession. First described by Drs Green and Solnit in 1964, multiple pediatric leaders have written about and studied this concept, which describes a discordance between the perceptions of the parent and the physician and the child's vulnerability to illness. There is a validated tool, the Vulnerable Child Scale, which may aid clinicians in determining risk. The etiology of VCS is multifactorial, with parental and child characteristics. Yet, physicians must be careful not to inadvertently add to these parental perceptions by saying things such as "lucky you came in just in time" or to dramatize events. This *In Brief* reminded me of a family I worked with during the first half of my career. Despite my best efforts to support and reassure this patient's mother, she thought her child was more ill than I perceived. This can create dissonance with our commitment to family-centered care and our underlying belief that parents know their child best. This patient had developed a fever on day 3 after birth and required hospitalization along with the long-awaited birth after infertility, both risk factors discussed in the literature. After I had cared for him from birth until 8 years of age, practiced cognitive reframing, and encouraged his mother to receive additional support through mental health counseling, his mother decided to seek a new pediatrician. This was very difficult for me and made me rethink much of my decision making, but I had reached a point where I felt that further evaluation or treatments for some of the reasons his mother brought him in were not in consonant with best practice standards or healthy for her son. Although this patient's father was involved, he deferred to his wife for the medical decision making. Well, imagine my surprise when 7 years later I received an unsolicited letter from his mother, apologizing that she had left my practice, acknowledging anxiety and fear on her part in assessing her son's vulnerability, and now understanding that I was trying to provide the best care to her son and their family. I tell this story because sometimes the outcome with patients and families is not what we expect in our profession, yet sometimes we receive an explanation and validation. But not always…

– Janet R. Serwint, MD
Associate Editor, *In Brief*

Vulnerable Child Syndrome

Kristine Schmitz

Pediatrics in Review 2019;40;313
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Achondroplasia

Elaine Pereira, MD*
*NewYork-Presbyterian Morgan Stanley Children's Hospital, Columbia University Medical Center, New York, NY

Achondroplasia is one of the most common and recognized short-limbed skeletal dysplasias, with a prevalence of 1 in 26,000 to 28,000 live births. Although achondroplasia is inherited in an autosomal dominant manner, 80% of affected children have a de novo mutation. The *FGFR3* gene is the only gene associated with achondroplasia. Two mutations in this gene account for 99% of cases; both result in an amino acid change (glycine to arginine), which results in continuous activation of the FGFR3 protein. Having a constantly active FGFR3 protein leads to the inhibition of chondrocyte proliferation, which, in turn, inhibits bone growth. The average adult height for patients with achondroplasia is 131 cm for a man and 124 cm for a woman.

Achondroplasia should be considered prenatally if shortened long bones (usually <5th percentile) are noted on third trimester ultrasonography. Some studies have seen a distinctive "collar hoop" sign wherein there is a small bony protuberance at the interface between the femoral metaphysis and the diaphysis. The metaphysis is poorly ossified as well. Prenatal molecular testing of *FGFR3* can confirm the diagnosis.

A neonate with achondroplasia may have physical features that are characteristic of the condition: rhizomelic (proximal) shortening of the upper and lower extremities, with extra skin creases at the knees and elbows; short fingers with a trident configuration of the hand (the second, third, and fourth digits seem similar in length and are splayed); and macrocephaly with frontal bossing and a depressed nasal bridge. Because 20% of neonates with achondroplasia may not have these characteristic features, a skeletal survey should be performed if there is any suspicion for this condition: radiographic abnormalities include metaphyseal changes, rhizomelic shortening, a relatively large cranial vault with a small base of the skull, small squared iliac wings, anteroposterior rib narrowing, and posterior vertebral scalloping.

Early diagnosis is critical because 5% to 10% of infants with achondroplasia experience serious medical problems, such as central apnea and high cervical myelopathy, both of which are secondary to a small foramen magnum. Because the base of the skull is smaller than normal, arterial compression at the level of the foramen magnum can also occur. With a smaller foramen magnum, an affected infant should not be put in a swing or a bouncer.

Infants with achondroplasia require a thorough neurologic examination and neuroimaging with head computed tomography or magnetic resonance imaging. Standard measurements for children with achondroplasia have been established for computed tomography, and the foramen magnum can be seen, but magnetic resonance imaging can better visualize the brain stem and cervical spinal cord. Neurosurgical consultation is advised if any major abnormalities appear on imaging. Polysomnography is likewise indicated because of the risk of obstructive sleep apnea.

AUTHOR DISCLOSURE Dr Pereira has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Frequent monitoring of head circumference is important during the first 2 years after birth because hydrocephalus can develop. If the head circumference rapidly crosses percentiles or if neurologic abnormalities such as lethargy or irritability appear, further imaging may be prudent. Interpretation of such imaging should be guided by the knowledge that extra-axial fluid and ventriculomegaly are common in children with achondroplasia and are usually benign. Also, infants and children with achondroplasia sweat more than the general population, and notable sweating should not be interpreted as a neurologic or cardiac problem if it is the only symptom.

Children with achondroplasia are at risk for orthopedic complications. Thoracolumbar kyphosis is seen in 90% to 95% of these patients. Infants need support to sit until they have the truncal muscle strength to maintain themselves, and soft strollers should be avoided. If the kyphosis is severe, an early orthopedic consultation may be appropriate. Children with achondroplasia typically walk by 2.5 years old. As the child begins to bear weight and walk, the kyphosis (if not severe) usually resolves. External rotation of the hips, a normal feature in infants with achondroplasia, should self-correct within 6 months of weightbearing. Although there can be some bowing of the legs, an orthopedic consult is warranted for chronic pain or a positional deformity that leads to difficulty walking. A general orthopedic evaluation should be considered when the child is 5 years old.

Obstructive sleep apnea has a prevalence of 10% to 87% in patients with achondroplasia. More commonly seen in older children and adults, it is secondary to adenoidal and tonsillar hypertrophy and midfacial retrusion that decreases the size of the airway. Obesity increases the risk, so avoiding excessive weight gain is an important preventive measure.

In the absence of neurologic compromise, people with achondroplasia have normal intelligence, but developmental milestones are delayed. Standardized developmental milestones and condition-specific growth curves are available for children with achondroplasia. Yearly hearing tests are recommended to check for conductive hearing loss. Occupational therapy from an early age can help affected children use adaptive aids for both the home and school settings. Foot support is important to keep the feet from dangling when the child is seated on a chair or toilet. Because of cervical spinal stenosis, collision sports and gymnastics are usually discouraged; noncontact activities such as swimming and biking are less likely to cause neurologic complications.

Females with achondroplasia are at increased risk for uterine fibroids, so oral contraception, which can worsen fibroids, should be avoided for long-term use. Consultation with a gynecologist or an adolescent medicine provider well versed in contraceptive methods can be helpful. Any pregnancy should be considered high risk. Baseline respiratory function studies should be performed early in pregnancy because respiratory compromise can develop over time. Cesarean delivery is usually advised because a small pelvic outlet and spinal stenosis make vaginal delivery dangerous for most women with achondroplasia.

A child born to a parent with achondroplasia has a 50% chance of inheriting the *FGFR3* gene mutation and having achondroplasia. If both partners have achondroplasia, each fetus has a 25% chance of having a homozygous mutation that is not compatible with life, a 50% of having achondroplasia; and a 25% chance of having normal stature. If one partner has achondroplasia and the other has a different skeletal dysplasia, each child has a 25% chance of having normal stature, a 25% chance of having achondroplasia, a 25% chance of having the other skeletal dysplasia, and a 25% chance of inheriting both pathogenic variants, which can lead to a different phenotype and different clinical features. Prenatal genetic counseling is recommended to clarify reproductive options and outcomes.

Currently, no medications or supplementations are recommended as treatment for achondroplasia. Several clinical trials are underway to determine whether growth hormone can be effective at increasing final height, but as yet no compelling evidence establishes real benefit. Whether the benefits of limb-lengthening techniques outweigh their limitations is questionable.

Pediatricians caring for children with achondroplasia should be prepared at each visit to provide both practical advice and emotional support. If possible, the child's home should be fitted with helpful adaptations such as lowered door handles and light switches. Although some physical accommodations will be necessary in school for classroom seating, toileting, and moving from class to class, other special privileges are not routinely needed. Importantly, as the child reaches school age, discussions should address how to talk to other children about short stature. Most patients with achondroplasia can live independent and fulfilled lives, so children with achondroplasia and their families should be encouraged to facilitate the strengths needed for independent living. The Little People of America

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(http://www.lpaonline.org/) is a wonderful resource for patients and families for emotional support.

COMMENT: In an age when social media has helped make bullying rampant, children perceived as “different” become tempting targets for abuse. Children with achondroplasia are no different from their peers in their intelligence and their sensitivities, in all the inner qualities that make each of us who we most essentially are. But to the eye of the beholder who looks for the opportunity to taunt, markedly short stature is an open invitation to exploit. The children, their families, and their teachers all need to be aware of this sad reality. Strategies aimed at prevention, especially at school, and at support in the face of physical and cyber bullying are essential to the care we give. Children who are victims of bullying are likewise at risk for depression, anxiety, drug use, and suicide, all of which warrant appropriate screening.

– Henry M. Adam, MD
Associate Editor, *In Brief*

Clarification

In the print version of the April 2019 review “Tuberculosis in Children” (Holmberg PJ, Temesgen Z, Banerjee R. *Pediatr Rev.* 2019 Apr;40(4):168-178; doi: 10.1542/pir.2018-0093), the second sentence under the section “Treatment of LTBI in Children,” on page 174 describes a recommendation that has changed. This sentence should read, Any of these regimens is considered adequate, but most experts prefer the shorter regimens. (28)” The online version of the article has been updated, and a clarification notice has been posted with the online version of the article.

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Achondroplasia

Elaine Pereira

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Although for many there may be obvious physical findings, having the accuracy of genetic testing is helpful for precision of diagnosis, for better understanding of the pathophysiology and long-term manifestations of the disease, and for genetic counseling. Primary care providers will benefit from consulting with radiologists and geneticists in making the diagnosis and in counseling patients and families. Patients, families, and providers alike may benefit from advocacy groups such as Little People of America, which can provide not only medical information, psychosocial support, and understanding of some of the challenges but also useful strategies for everyday life.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

Correction

An error appeared in the print version of the June 2019 *In Brief* "Achondroplasia" (Pereira E. *Pediatr Rev.* 2019;40(6): 316-318; doi: 10.1542/pir.2018-0009). The second sentence of the second paragraph should read: "Some studies have seen a distinctive 'collar hoop' sign wherein there is a small bony protuberance at the interface between the femoral metaphysis and the diaphysis." The online version of the article has been corrected, and a correction notice has been posted with the online version of the article. The journal regrets the error.

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Achondroplasia

Elaine Pereira

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Visual Diagnosis

Acute-Onset Headache, Vertigo, and Torsional Nystagmus in a 13-year-old Boy

Helen Wu, MS,* Amanda Weber, DO,† Asri Yuliati, MD†

**MD/PhD Program, and †Department of Neurology, Children's Hospital of Michigan, Detroit Medical Center, Wayne State University School of Medicine, Detroit, MI*

PRESENTATION

A 13-year-old boy presents to the emergency department with a 4-day history of new-onset severe bifrontal aching headache with associated nausea, vomiting, photophobia, phonophobia, and vertigo. He had been evaluated at another institution twice in the preceding 4 days for the same complaint, and he failed outpatient management with naproxen and meclizine. His previous medical history is unremarkable. He denies drug use. The emergency department administers a migraine cocktail consisting of ketorolac, diphenhydramine, and prochlorperazine, which results in significant pain improvement, but the vertigo persists.

On physical examination, vital signs and results of pulmonary, cardiac, gastrointestinal, and skin examinations are normal. He is awake, alert, and oriented. His neurologic examination is remarkable for a rightward head tilt, torsional nystagmus (Video), dysmetria with finger-to-nose evaluation greater on the left, and difficulty with tandem gait. He is able to ambulate independently. Reflexes and sensory examination findings are normal. Due to nystagmus, the funduscopic examination cannot be completed. Basic laboratory electrolyte panel and complete blood cell count are noncontributory. Magnetic resonance imaging (MRI) is ordered emergently and reveals the diagnosis.

DIAGNOSIS

Based on his physical examination and laboratory findings, the differential diagnosis for the patient's complaints includes a brainstem or cerebellar stroke, mass, vascular malformation, basilar migraine, or primary vestibular problem. The constellation of severe headache with new focal neurologic findings prompts an urgent evaluation for structural abnormalities.

The brain MRI with and without contrast reveals a heterogeneous lesion measuring 9.4 × 8.0 × 8.5 mm, which is hyperintense on T1, hypointense on T2 and T2–fluid-attenuated inversion recovery sequences, and has significant gradient susceptibility in the left cerebellar peduncle at the level of the left facial colliculus (Fig). These features are consistent with a cavernous malformation (CM). The T1 and T2 characteristics of the lesion are consistent with the presence of a subacute hemorrhage, likely spontaneous in nature. Its presence would also explain the presenting symptoms and the focal neurologic deficits found in this patient. There is an associated cluster of 3 large veins, suggestive of surrounding developmental venous anomalies (DVAs) (Fig A).

AUTHOR DISCLOSURE Ms Wu and Drs Weber and Yuliati have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Video. The patient demonstrated subtle rotational nystagmus with leftward fast component.

DISCUSSION

CMs, or cavernomas, are vascular abnormalities consisting of dilated thin-walled capillaries without associated smooth muscle or intervening brain tissue. They are slow-flow lesions and may be associated with DVAs in up to 25% of patients. DVAs are congenital variants of cerebral veins characterized by a convergence of multiple venules into a dilated collector vein, which drains either superficially or into the deep subependymal venous systems or both. DVAs are often asymptomatic unless associated with CMs or arterial venous anomalies. Cerebral CMs have an increased risk of hemorrhage when they are associated with DVAs, particularly when they are located in the cerebellum or brain stem. Cavernous malformations occur most commonly in the supratentorial brain, and lesions in the infratentorial regions, including the brain stem and cerebellum, are less common.

Typical presenting symptoms of CMs include seizures; headaches; hydrocephalus; sensory, motor, and speech changes; ataxia; and other focal neurologic deficits. Supratentorial lesions are most commonly associated with new-onset seizures, whereas infratentorial lesions are more commonly associated with focal neurologic deficits (eg, cranial nerve palsy) or gait ataxia, as seen with this patient.

Cerebral CMs occur in approximately 0.5% of the population, with approximately equal frequency in boys and girls. Cerebral CMs are the second most common vascular abnormality, after aneurysms, found on brain MRIs. In the pediatric population, they tend to occur in a bimodal distribution, with the first peak occurring between birth and 2 years of age and the second peak between ages 12 and 16 years. They may occur sporadically or in an autosomal dominant fashion. Familial cerebral CMs are associated with mutations in *KRIT1* (*CCM1*), *CCM2*, and *PDCD10* (*CCM3*) and are noted to be more common in Hispanic Americans. The familial forms tend to present with multiple, bilateral cavernous angiomas and may involve areas outside of the brain, such as the retina. In contrast, sporadic cases most commonly present with solitary lesions. Radiation exposure may also induce the development of vascular lesions, including CMs, vasculopathies, and neoangiogenesis. Younger age at time of exposure and larger radiation doses increase the risk of vascular lesion formation.

The characteristic MRI appearance of a CM is a well-circumscribed, heterogeneous, "popcorn-like" lesion. Evolving blood products cause varying T1 and T2 signal intensities. There is often a surrounding hemosiderin ring as a result of remote hemorrhage and chronic leakage of red blood cells into the lesion and surrounding tissue.

CMs are associated with increased risk of hemorrhage over time. A meta-analysis by Horne et al estimated an

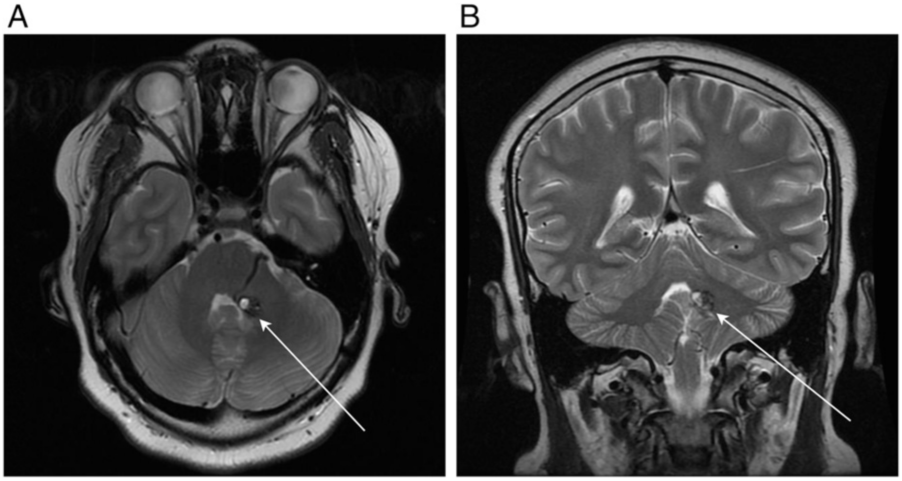

Figure. Axial (A) and coronal (B) magnetic resonance images show a lesion (arrows) demonstrating T1 hyperintensity, T2 hypointensity, and significant gradient susceptibility in the left middle cerebellar peduncle. The lesion and the associated cluster of veins (A) are suggestive of cavernous malformation with associated developmental venous anomaly.

intracranial hemorrhage risk of approximately 15.8% within 5 years of presentation. Patients with symptomatic brainstem lesions demonstrated the highest 5-year risk for hemorrhage (30.8%). Asymptomatic individuals with supratentorial lesions had the lowest 5-year risk of hemorrhage (3.8%). Gross et al showed a similar pattern in children, where brainstem lesions had the highest annual hemorrhage rate (16.7%) compared with those with asymptomatic incidental lesion findings (0.5%). History of previous hemorrhage, location in the brain stem, and presence of associated DVAs all increased the risk of hemorrhage.

Close observation is recommended in patients with asymptomatic lesions, and conservative management is recommended for patients after the first brainstem CM hemorrhage because they may have a benign course. Patients with 2 or more hemorrhages should be strongly considered for surgery because they are more likely to follow an aggressive course. Other indications for surgical resection can include life-threatening emergencies, refractory epilepsy, and progressive neurologic deficits. Unfortunately, due to location, brainstem lesions present a unique surgical challenge. Therefore, risks and benefits of surgical management should be carefully considered in patients with brainstem lesions.

Patient Course

The patient was evaluated by the neurosurgery team and received a short course of dexamethasone to reduce surrounding brain tissue edema and inflammation. Several days later, his symptoms improved, and he was discharged home with acetaminophen for symptomatic headache management and close neurosurgery follow-up. Repeated MRIs 2 and 6 weeks after presentation verified lesion stability with resolution of hemorrhage and surrounding edema. Given the improvement of his symptoms, no surgical intervention is planned at this time. He continues to receive physical therapy and vestibular rehabilitation for vertigo and gait dysfunction.

Summary

- A child presenting with headache and focal neurologic deficits needs a thorough evaluation, including detailed family history, neurologic examination, and imaging studies, to help delineate the cause.
- Cavernous malformations are the second most common vascular abnormality found on brain magnetic resonance imaging (MRI) and can present with a variety of symptoms, including new-onset seizure, headache, hydrocephalus, focal sensory, motor, language deficits, cranial nerve abnormalities, and ataxia.
- Brain MRI with and without contrast is the recommended imaging study for characterization of cerebral cavernous malformations and evaluation for associated developmental venous anomalies. An increased risk of hemorrhage is predicted by evidence of previous hemorrhage, location in the brain stem, and associated developmental venous anomalies.

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Visual Diagnosis: Acute-Onset Headache, Vertigo, and Torsional Nystagmus in a 13-year-old Boy

Helen Wu, Amanda Weber and Asri Yuliati

Pediatrics in Review 2019;40;e22
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Leukemia in Children

Joel A. Kaplan, DO, MPH

Department of Pediatrics, Atrium Health Levine Children's Hospital, Charlotte, NC

Practice Gaps

Persistent bone pain, limp, back pain, fever, headache, and symptoms of anemia and thrombocytopenia are common ways that pediatric leukemia presents. Many of these symptoms can be seen in common childhood illnesses, so a high index of suspicion in patients with persistent symptoms is required to make the diagnosis. The prognosis for these children is excellent, especially in acute lymphoblastic leukemia, but survivors of childhood leukemia need to be followed closely for long-term toxicities.

Objectives

After completing this article, readers should be able to:

1. Understand the incidence and general epidemiology of childhood leukemia, including syndromes that increase the risk of leukemia in children.
2. Recognize the clinical presentation of childhood leukemia and how this relates to proper interpretation of a complete blood cell count.
3. Understand the potential oncologic emergencies in childhood leukemia.
4. Describe the prognostic factors associated with precursor B-lymphoblastic leukemia, including an understanding of the importance of minimal residual disease.
5. Understand the importance of supportive care in the treatment of childhood acute myelogenous leukemia.
6. Describe the long-term complications of childhood leukemia treatment in the modern era.

AUTHOR DISCLOSURE Dr Kaplan has disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ALL	acute lymphoblastic leukemia
AML	acute myelogenous leukemia
BMT	bone marrow transplant
CBC	complete blood cell
CML	chronic myelogenous leukemia
CNS	central nervous system
DIC	disseminated intravascular coagulation
EFS	event-free survival
HLA	human leukocyte antigen
MRD	minimal residual disease
Ph	Philadelphia chromosome
TKI	tyrosine kinase inhibitor
WBC	white blood cell

INTRODUCTION

Leukemia is the most common malignancy of childhood, accounting for 30% of cases of childhood cancer. Although there are some associations between environmental or host factors, most leukemia diagnoses in children are sporadic. There are 3 main subtypes of leukemia: acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), and chronic myelogenous leukemia (CML). ALL is the most common subtype, accounting for approximately 80% of cases.

CML is the least common, and this review touches on this subtype only briefly. There are many subgroups within ALL and AML. These subgroups have variable biological features, prognoses, and treatment regimens. Children generally present with symptoms related to cytopenias or leukemic infiltration of the bone marrow. Other organs, such as the spleen, liver, testes, and central nervous system (CNS), can also be involved. With modern, risk-adapted therapy, most children are cured of their disease. Despite these successes, relapse continues to be a problem. However, we have entered an exciting time of targeted and immunologic therapy that is revolutionizing the treatment of these challenging patients. There are late effects of treatment, and these need to be recognized by the general pediatrician, with an understanding that these late effects are different among the many subtypes of leukemia.

EPIDEMIOLOGY

Childhood cancer is very rare, with approximately 14,000 cases diagnosed in children younger than 18 years in the United States annually. For perspective, there are 80,000 cases of prostate cancer diagnosed each year, which is only the fifth most common cancer in adults. In children, hematologic malignancies predominate, accounting for approximately one-third of all cases of childhood cancer. Cancer remains the most common cause of disease-related death in children. The incidence of ALL is approximately 30 cases per 1 million persons. This incidence varies among different ethnic groups. ALL is more common in white individuals compared with black individuals, with Hispanic people having the highest risk. (1)

Precursor B-cell ALL is much more common than T-cell disease, accounting for approximately 80% of cases of ALL. AML accounts for 18% of cases of childhood leukemia, and CML is very rare and tends to occur in adolescents. Outside of exposure to ionizing radiation, there are very few environmental factors that have shown a strong link with childhood leukemia. Monozygotic twins have a 10% to 15% concordance rate for ALL. The cause of ALL is most likely multifactorial, involving genetic, immunologic, and infectious factors that need further study. (2)

Patients with Down syndrome are at 15 times increased risk of developing leukemia compared with the general population. This risk is increased for both ALL and AML. (3) This is especially true in children with trisomy 21, who had transient myeloproliferative disorder as infants. In this population the risk of developing AML is 16% at a median age of 441 days. (4) Transient myeloproliferative disorder is characterized by peripheral blasts and hepatosplenomegaly in the newborn with trisomy 21. Most cases resolve spontaneously, but some require treatment with low-dose chemotherapy. Interestingly, patients with Down syndrome who develop AML have a favorable outcome compared with those without Down syndrome. Other syndromes, such as Fanconi anemia, Bloom syndrome, Klinefelter syndrome, and neurofibromatosis, are also associated with leukemia.

CLINICAL PRESENTATION

The most common presenting symptoms of leukemia result from the clonal proliferation of leukemic blasts in the bone marrow, preventing normal production of red blood cells, platelets, and neutrophils. The degree of anemia, thrombocytopenia, and neutropenia is highly variable. A significant anemia can cause pallor, fatigue, dyspnea on exertion, headache, dizziness, and near syncope. Although the thrombocytopenia can be severe, most patients with leukemia do not present with bleeding. Many patients can have bruising and petechiae, but serious bleeding is rare. Fevers are very common in patients with leukemia and should be part of the differential diagnosis of fever of unknown origin. Despite sometimes severe neutropenia, infection or sepsis at diagnosis is uncommon.

Children with leukemia have bone marrow that has been replaced with leukemic blasts. This expansion of the bone marrow cavity very commonly causes bone pain, limp, or refusal to walk. Back pain is also found, and a complete blood cell (CBC) count with a differential count should be considered as part of the evaluation of this complaint, along with close interval follow-up until the cause of the back pain is discovered. Patients with bone pain are frequently referred to orthopedics, where a diagnosis of leukemia is sometimes made when magnetic resonance imaging shows diffuse increased signal intensity in the bone marrow.

Leukemia can infiltrate other organs outside of the bone marrow, leading to lymphadenopathy, hepatomegaly, splenomegaly, and kidney lesions. The most impressive splenomegaly is seen with CML. The acute leukemias have variable spleen and liver size. Despite the hepatomegaly, liver dysfunction is uncommon. Testicular disease occurs in approximately 2% of children with ALL. (5) This presents with a painless testicular mass or uniformly enlarged testes. CNS leukemia can be seen in both ALL and AML but is more common in the former. T-cell ALL has the highest risk of CNS disease. This can manifest itself as headache, seizure, visual changes, cranial nerve abnormalities, and change in mental status. CNS disease can also be asymptomatic.

The different types of leukemia tend to exhibit certain features in their clinical presentation. Infantile ALL, defined as leukemia presenting before 1 year of age, tends to present with very high white blood cell (WBC) counts. When an adolescent male presents with a high WBC count and an anterior mediastinal mass, T-cell ALL should be considered. These patients frequently can have difficulty breathing, especially in the supine position. This can be a medical emergency, and airway management can be difficult. CML can have extremely high WBC or platelet counts, with massive splenomegaly. Acute promyelocytic leukemia, a rare subtype of AML, is strongly associated with bleeding, CNS hemorrhage, and disseminated intravascular coagulation (DIC) at diagnosis. Chloromas are extramedullary collections of leukemic blasts that can occur anywhere in the body, more often in soft tissues and the CNS. They tend to occur more often in AML with monocytic differentiation. Children with trisomy 21 and AML tend to present with isolated thrombocytopenia, many times after a history of transient myeloproliferative disorder.

DIAGNOSIS

It is very important for a pediatrician to understand the proper interpretation of a CBC count with differential count. It is easy to think of a CBC count as a measure of bone marrow function. The marrow produces red blood cells, neutrophils, and platelets. A cytopenia reflects poor marrow function or peripheral destruction of the involved cell. Most patients with leukemia have more than 1 cell line affected at diagnosis. If patients have isolated neutropenia, anemia, or thrombocytopenia, then an appropriate differential diagnosis should be formulated for the individual cytopenia. When more than 1 cell line is affected, the diagnosis of leukemia should be more strongly considered. Diagnoses that can be commonly confused with leukemia include viral suppression, drug-induced cytopenia, immune thrombocytopenic purpura, autoimmune hemolytic anemia or neutropenia, Evan syndrome, transient erythroblastopenia of childhood, aplastic anemia, splenic sequestration, and juvenile idiopathic rheumatoid arthritis.

A bone marrow aspirate is necessary to definitively diagnose leukemia. The diagnosis can also be made from peripheral blood if a sufficient number of blasts are present. This can be helpful in cases where the WBC count is high and making a diagnosis quickly is advantageous. Both morphologic analysis and flow cytometry are used to evaluate the bone marrow. Morphologic analysis evaluates the marrow and leukemic blasts under the microscope (Fig 1). Flow cytometry uses immunophenotypic characteristics to differentiate between the different types of leukemia. ALL and AML can sometimes be differentiated using morphologic features alone, where T- and B-cell ALL look identical under the microscope. The different leukemias have distinctive immunophenotypic markers that can be found using flow cytometry. This modality is required for accurate

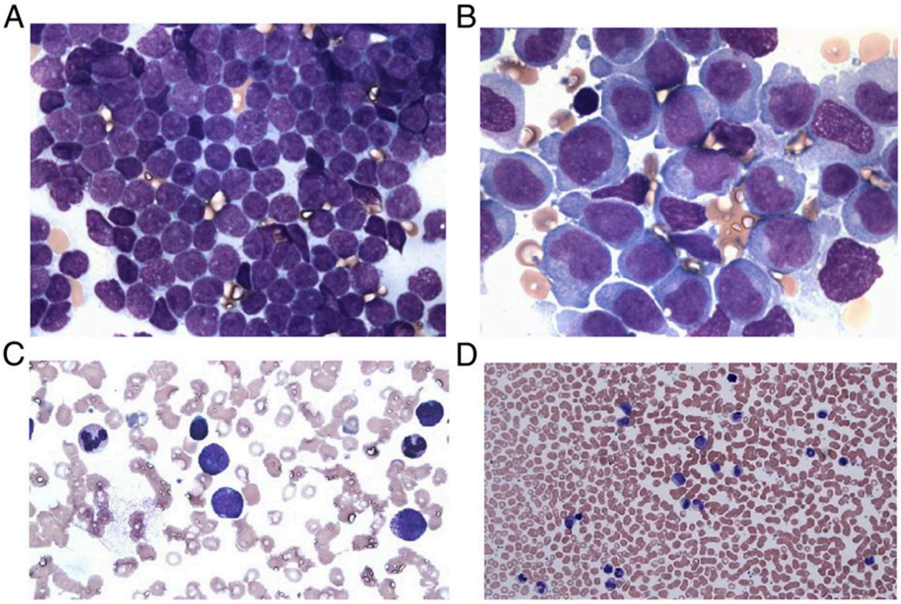


Figure 1. Photomicrographs of different types of leukemia. A. Acute lymphoblastic leukemia. Notice the high nucleus to cytoplasm ratio and uniform-appearing blasts. This morphologic profile is commonly seen in both T- and B-cell leukemia. B. Acute myelogenous leukemia, monocytic subtype. Notice the relatively increased cytoplasm and nuclear indentation. C. Acute promyelocytic leukemia. In the blast on the lower right of the field notice the increased cytoplasm with prominent granules. D. Chronic myelogenous leukemia. Notice the increased number of myeloid progenitors at various stages of differentiation.

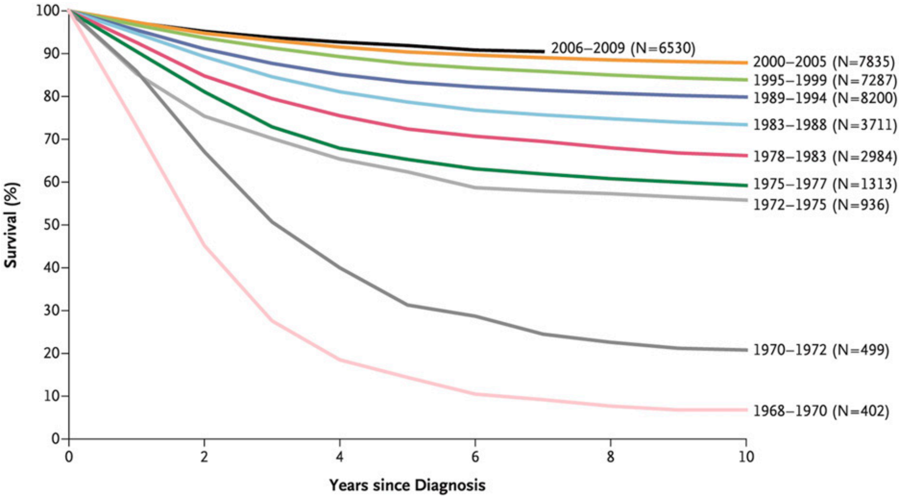


Figure 2. Overall survival among children with acute lymphoblastic leukemia who were enrolled in Children's Cancer Group and Children's Oncology Group clinical trials, 1968–2009. Reprinted with permission from Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med.* 2015;373(16):1541–1552.

diagnosis. (6) CML has very distinctive characteristics and can be diagnosed using morphologic analysis alone. It is characterized by a proliferation of normal hematopoietic progenitor cells seen in the peripheral blood. All patients with acute leukemia require a lumbar puncture with cerebrospinal fluid sampling to rule out CNS disease. If neurologic symptoms, severe headache, or cranial nerve palsies are present at diagnosis, magnetic resonance imaging may also be necessary. A thorough testicular physical examination should be performed in all male patients.

ONCOLOGIC EMERGENCIES IN NEWLY DIAGNOSED LEUKEMIA

Hyperleukocytosis can be seen in any patient with leukemia and is generally defined as a WBC count of greater than 100,000/μL (>100×10^9/L). This is more common in those with AML, T-cell ALL, and infantile leukemia. The large number of blasts can cause leukostasis, which precipitates decreased tissue perfusion. This is a medical emergency causing neurologic and pulmonary sequelae. Patients with AML have more problems with leukostasis, at lower WBC counts, because AML blasts are larger and stickier. Those with ALL generally only develop signs of leukostasis with extremely high WBC counts.

Signs and symptoms of leukostasis include the following: neurologic—headache, confusion, lethargy, dizziness, blurry vision, ataxia, papilledema, retinal hemorrhage, and CNS hemorrhage; respiratory—tachypnea, hypoxia, infiltrates on chest radiography, respiratory failure, and acute respiratory distress syndrome; vascular—peripheral vascular occlusion and thrombosis; and coagulation—DIC, abnormal tests of coagulation with elevated prothrombin and partial thromboplastin times with a decreased fibrinogen level.

These patients are also at risk for tumor lysis syndrome, defined as hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia. Tumor lysis syndrome usually develops after therapy is started but can occur at initial presentation. It is caused by the intracellular contents of malignant cells being spilled into the circulation. This can overwhelm the kidney's ability to process the released nucleic acids, potassium, and phosphorus. Without prompt intervention this can lead to cardiac arrhythmias and renal failure. The management of hyperleukocytosis includes the following:

- Place 2 large-bore peripheral intravenous lines if the patient does not yet have a central line.
- Hydrate with dextrose 5% half-normal saline at 125 mL/m^2 per hour. No potassium should be put in intravenous fluids.
- Begin allopurinol therapy.
- Consider rasburicase if the uric acid level is greater than 8.0 mg/dL (>476 μmol/L)
- Every-6-hour renal function panel and uric acid level.
- Transfuse platelets if less than 30×10^3/μL (<30×10^9/L)
- Transfuse fresh frozen plasma and cryoprecipitate for abnormal coagulation studies or DIC.
- Avoid packed red blood cell transfusion if possible. If indicated, start with low volumes.
- Treat tumor lysis syndrome if present.
- Begin induction chemotherapy as soon as possible.
- Early consultation with pediatric nephrology.

The use of leukapheresis has fallen out of favor in patients with hyperleukocytosis. This therapy requires central line access, significant planning with the blood bank, and resources, all delaying definitive therapy. Leukapheresis is also of questionable benefit in these patients and carries its own risks. (7) Therefore, induction chemotherapy should be started as soon as possible. If delayed, cytoreduction can be achieved with hydroxyurea or corticosteroids, the latter being used only with a known diagnosis of ALL. Leukapheresis is reserved for patients who have persistent or worsening symptoms of leukostasis despite appropriate attempts at cytoreduction.

T-cell ALL is commonly associated with an anterior mediastinal mass. This mass can be very large and cause significant symptoms, including dyspnea on exertion, shortness of breath, tachypnea, orthopnea, and stridor. Patients with significant respiratory compromise require admission to the ICU and prompt initiation of leukemia-directed therapy. Reduction in size of the mass can be achieved with the use of corticosteroids alone, and responses are usually prompt, avoiding the need for intubation. Induction therapy should be started after definitive diagnosis is made.

Acute promyelocytic leukemia is a very rare subtype of AML that is associated with severe coagulopathy. Patients can present with DIC, bleeding, and thrombosis. Prompt diagnosis is necessary and can be done preliminarily using morphologic analysis alone (Fig 1). Left untreated, patients can develop pulmonary or cerebrovascular catastrophic bleeding. Platelet counts should be maintained at greater than $50 \times 10^3/\mu L$ ($>50 \times 10^9/L$) and coagulation abnormalities treated with fresh frozen plasma and cryoprecipitate, the latter being used for hypofibrinogenemia. Leukapheresis is contraindicated in these patients.

THERAPY

Acute Lymphoblastic Leukemia

ALL is a rapidly progressive disease that causes excess, very immature WBCs called *blasts* to proliferate in the bone marrow at the expense of normal hematopoietic cells. The bone marrow can then no longer produce adequate red blood cells, platelets, and neutrophils. The cell of origin of these blasts is in the lymphocyte developmental line and can infiltrate the CNS, peripheral blood, lymph nodes, spleen, liver, and kidneys. Childhood ALL was an almost universally fatal disease in the 1960s. It is now one of the most curable diseases seen in pediatric oncology, with an event-free survival (EFS) of approximately 90%. In fact, there are subsets of ALL in children younger than 10 years that have an EFS of close to 100%. These advances can be attributed to the success of cooperative group trials. These trials allowed for study of a rare disease that otherwise would not have been possible (Fig 2). Multiagent chemotherapy has been improved by identifying risk groups with variable prognosis and tailoring therapy to individual patients. (8) This is based on patient characteristics, biological factors, and degree of response to initial treatment. At diagnosis, patients are classified as either standard risk or high risk based on criteria from the National Cancer Institute. Standard-risk patients are aged 1 to 10 years, have WBC counts less than $50,000/\mu L$ ($<50 \times 10^9/L$), are of B-cell origin, and do not have CNS or testicular disease (Table 1). To be high risk requires only 1 discordant criteria. Treatment of childhood leukemia is truly a team effort. It requires all the resources of a children's hospital along with specialized physicians across multiple disciplines, advanced care practitioners, nurses, nurse navigators, social workers, psychologists, pharmacists, and research support.

The following types of ALL are treated on different treatment regimens: precursor B cell, T cell, Philadelphia chromosome (Ph) positive, and infantile.

Minimal residual disease (MRD) testing allows for the accurate detection of very small amounts of leukemic blasts in the bone marrow. MRD has been shown to be a strong prognostic indicator across all leukemia subtypes. Historically, remission was defined as having less than 5% blasts in the bone marrow by morphologic analysis alone after initial induction chemotherapy. This has been largely replaced with the use of MRD testing of the bone marrow at the end of induction using flow cytometry. Clinical trials in precursor B-cell ALL showed that MRD was highly prognostic. More than 2,000 children were studied, with a significant EFS advantage even in patients with negative MRD compared with those with low-level MRD of 0.01% to 0.1% (EFS: 88% versus 59%). This advantage was seen in all risk groups. (9) The use of MRD is also prognostic in T-cell, Ph-positive, infantile, and relapsed ALL.

Precursor B-cell ALL is treated with multiagent chemotherapy in 5 phases: induction, consolidation, interim maintenance, delayed intensification, and maintenance (Table 2). The total time of therapy is approximately 2 to 3 years for boys and 2 years for girls. The intensity of therapy is individualized based on the final risk group designation. High-risk patients receive a more intensive therapy compared with standard-risk patients. Much of the treatment time is spent in maintenance, which is the least intensive phase of therapy. During maintenance, patients receive oral mercaptopurine and methotrexate. A 5-day corticosteroid pulse and vincristine are used variably depending on the regimen. During maintenance it is impossible to tell that a

TABLE 1. **Prognostic Factors in Precursor B-cell Acute Lymphoblastic Leukemia**

PROGNOSTIC FACTOR	LOW RISK (EFS ~98%)	STANDARD RISK (EFS ~95%)	HIGH RISK[a] (EFS ~60%–95%)
Age, y	1–9.99	1–9.99 y	≥10
White blood cell count at diagnosis, /μL (×10^9/L)	<50,000 (<50)	<50,000 (<50)	≥50,000 (≥50)
Central nervous system status	Negative	Negative	Positive
Testicular disease	No	No	Yes
Cytogenetics (detects genetic alterations in leukemic cells)	ETV6-RUNX1 or trisomy 4 and 10	No genetic alteration or a genetic alteration present with no prognostic significance	IAMP21, MLL, hypodiploid, t(9;22) translocation
Minimal residual disease at day 29 of induction, %	<0.01	<0.01	≥0.01

EFS=event-free survival.

[a] Only 1 factor required.

patient is being treated for leukemia. Children return to school, adolescents return to sports, and young adults return to work. Compliance with mercaptopurine and methotrexate therapy is extremely important and has prognostic significance. (10) In difficult social situations and in the adolescent and young adult population this can be challenging and requires a team approach to ensure compliance. CNS disease is rare at diagnosis, but CNS prophylaxis is required to prevent subsequent CNS relapse. This is done through the instillation of methotrexate into the cerebrospinal fluid at multiple time points throughout treatment. Without this prophylaxis, the CNS relapse rate is approximately 50%. Cranial radiation is reserved for only the very few patients who present with CNS disease at diagnosis.

T-cell ALL historically was considered to have a poor prognosis compared with precursor B-cell leukemia, and a higher percentage of patients were treated with cranial radiation for CNS prophylaxis. With modern treatment regimens this difference has been largely eliminated. (11) The treatment of T-cell disease is very similar to that of high-risk precursor B-cell ALL. CNS prophylaxis is especially important for this population because CNS disease is more common. With the current protocols, only a very small number of patients require cranial radiation.

Ph-positive ALL (*BCR-ABL1* positive) and infantile ALL make up a very small percentage of childhood leukemias and are treated with separate protocols. Until recently, Ph-positive ALL was treated with bone marrow transplant (BMT) in first remission. In the era of tyrosine kinase inhibitors (TKIs), many patients can be cured with chemotherapy alone. (12) Infants with ALL are an especially challenging group of patients to treat. They have unique molecular characteristics as most patients have the mixed lineage leukemia rearrangement gene and are very young. Infants who are older than 6 months tend not to have this molecular abnormality and have a significantly better prognosis. Disease control can be challenging because infants tend to relapse early on in therapy and are difficult to get back into remission. New agents are required to improve survival in this patient population.

Ph-like ALL is characterized by gene expression similar to that of the Ph (*BCR-ABL1*–positive ALL). It was recently discovered that approximately 15% of patients with high-risk ALL harbor these mutations. These patients were also found to have an inferior prognosis compared with those without Ph-like rearrangements (EFS: 63% versus 86%). (13) Current research is aimed at targeting these mutations to improve EFS.

All patients with ALL require prophylaxis for *Pneumocystis carinii* pneumonia. First-line therapy is trimethoprim-sulfamethoxazole. If the patient has an allergy or does not tolerate this medication secondary to myelosuppression, alternatives include dapsone, inhaled pentamidine, and atovaquone. Dapsone has the relatively common adverse effect of methemoglobinemia, and inhaled pentamidine can sometimes cause bronchospasm, which can be prevented with albuterol nebulization. Atovaquone is rarely used. Vaccinations should be avoided during treatment except for the influenza vaccine. Vaccinations of siblings of patients with leukemia can be completed on a normal schedule. Any

TABLE 2. **Drugs Used in the Treatment of Acute Lymphoblastic Leukemia as per Children's Oncology Group Regimens**

TREATMENT PHASE	DRUGS	ADVERSE EFFECTS
Induction	Vincristine Dexamethasone/prednisone Pegylated asparaginase Daunorubicin (not in standard risk) Intrathecal cytarabine/methotrexate	Constipation, peripheral neuropathy, hypertension, hyperglycemia, infection (including invasive fungal), poor wound healing, anaphylaxis, thrombosis, pancreatitis, myelosuppression, cardiomyopathy, methotrexate neurotoxicity
Consolidation (combination varies by risk group)	Standard risk: 6-Mercaptopurine Vincristine Intrathecal methotrexate High risk: 6-Mercaptopurine Vincristine Cyclophosphamide Cytarabine Pegylated asparaginase Intrathecal methotrexate	Significant myelosuppression with transfusion requirements in high risk, infection (including invasive fungal in high risk), peripheral neuropathy, constipation, fever, myalgias, rash, anaphylaxis, thrombosis, pancreatitis, methotrexate neurotoxicity
Interim maintenance	Standard risk: Intravenous methotrexate (escalating dose) Vincristine Intrathecal methotrexate High risk: Intravenous methotrexate (high dose) Vincristine Intrathecal methotrexate	Mucositis, renal insufficiency, myelosuppression, constipation, peripheral neuropathy, neurotoxicity
Delayed intensification	Vincristine Decadron Pegylated asparaginase Daunorubicin 6-Thioguanine Vincristine Cyclophosphamide Cytarabine Pegylated asparaginase Intrathecal methotrexate	Significant myelosuppression with transfusion requirements in all patients, sinusoidal obstructive syndrome of the liver, infection (including invasive fungal), peripheral neuropathy, constipation, fever, myalgias, rash, anaphylaxis, thrombosis, pancreatitis, methotrexate neurotoxicity
Maintenance	6-Mercaptopurine Oral methotrexate Vincristine Dexamethasone/prednisone pulses Intrathecal methotrexate	Neutropenia, avascular necrosis (osteonecrosis), knees and hips most often, peripheral neuropathy, constipation, methotrexate neurotoxicity

exposure to varicella zoster, measles, or other significant virus can be serious, and patients should be referred to the treating institution immediately for infectious disease consultation. Fever should always be taken seriously, with blood cultures collected from the central line and early institution of broad spectrum antibiotics.

Relapsed ALL continues to be a therapeutic challenge, and many patients die of their disease. Depending on timing and site of relapse, some patients can be cured with very intensive chemotherapeutic regimens. Patients who relapse late with isolated disease in the CNS or testes have the best prognosis. Those who relapse early in the bone marrow or have T-cell disease have the worst outcomes. Many relapsed patients require BMT for a chance at definitive cure.

Targeted immunotherapy is revolutionizing the treatment of relapsed patients with precursor B-cell ALL (Table 3).(14)(15)(16)(17)(18) Leukemic blasts express CD19, CD20, and CD22 on their surface, and these antigens are not expressed on many other cells, making them attractive targets for therapy. These drugs include the bispecific T-cell–engaging antibody blinatumamab, the anti-CD22 antibody drug conjugate inotuzumab, and chimeric antigen receptor T-cell therapy. These treatments have shown excellent results in very heavily pretreated patients with acceptable toxicity profiles. In the next generation of

TABLE 3. **Targeted Therapies in ALL**

AGENT	MECHANISM OF ACTION	CLNICAL EFFICACY	FUTURE RESEARCH
Blinatumomab	Bispecific T-cell engager antibody targeting CD19	Study of heavily pretreated adults with persistent minimal residual disease: 16 of 21 patients became minimal residual disease negative (14) 39% complete response rate in relapsed/refractory children (15)	Ongoing randomized trial in relapsed ALL Possible use in future trials in newly diagnosed patients
Inotuzumab ozogamycin	Monoclonal antibody-drug conjugate targeting CD22	INOVATE trial in relapsed adult patients had a complete response rate of 81% (16) Retrospective data only in children	Ongoing single-agent trial in relapsed ALL Possible use in future trials in newly diagnosed patients
Chimeric antigen receptor T-cell therapy	Reprogramming of T cells to identify malignant cells with tumor-specific antigen recognition (17) Can target CD19, CD22, or both	Excellent activity with complete response rates of 70%–90% in heavily pretreated patients (18)	Multiple ongoing trials for relapse Possible use in refractory or newly diagnosed patients at very high risk for relapse
Imatinib/dasatinib	Tyrosine kinase inhibitors	Excellent efficacy in newly diagnosed patients with Ph-positive ALL Case reports of use in newly diagnosed patients with Ph-like ALL	Ongoing nonrandomized trial in newly diagnosed patients with Ph-like ALL
Ruxolitinib	Janus kinase 1 and 2 inhibitors	Phase 1 study as a single agent in relapsed solid tumors and leukemia in children (18)	Ongoing nonrandomized trial in newly diagnosed patients with Ph-like ALL (*CRLF2* and *JAK1/2* mutations)

ALL=acute lymphoblastic leukemia, Ph=Philadelphia chromosome.

precursor B-cell ALL trials, these agents will be evaluated in the upfront setting.

Acute Myelogenous Leukemia

AML is also a rapidly progressive disease. Excess blasts proliferate in the bone marrow as well as in the blood and can affect multiple organ systems. The cell of origin is in the myeloid line. Granulocytes, monocytes, erythrocytes, and megakaryocytes can all be the immature cell of origin, creating the varied morphologic appearance of this disease. AML has seen a significant improvement in survival, albeit not to the same degree as with ALL. Relapse-free survival of patients with AML is approximately 60%. This has been accomplished by intensifying chemotherapeutic regimens, delineating the appropriate use of BMT, and improving supportive care. Patients with favorable cytogenetic and molecular features and those who are MRD negative after induction can be treated with chemotherapy alone. Patients with unfavorable cytogenetics and molecular features or poor response to induction therapy require BMT. The group with the best prognosis has relapse-free survival of approximately 80%. Other groups can have relapse-free survival as low as 20%.

Patients who do not require a BMT are treated with 4 to 5 cycles of chemotherapy. In many patients, the first 2 cycles use a combination of cytarabine, etoposide, and daunorubicin. MRD is measured at the end of cycle 1. The remaining chemotherapy is based on high-dose cytarabine, which has long been recognized as an excellent drug for the treatment of AML. CNS prophylaxis is required with intrathecal cytarabine.

Patients with poor risk features require a BMT. This is usually performed after the third cycle of chemotherapy but can vary between institutions and therapeutic trials. BMT works best if the patient is MRD negative, but this is not always possible to achieve in children whose disease is very difficult to treat. Some patients can undergo BMT with MRD-positive disease and be cured.

The possible donor sources for BMT include human leukocyte antigen (HLA)–identical sibling, HLA-matched unrelated donor, HLA-mismatched unrelated donor, haploidentical (half-match) from a parent or sibling, and cord blood.

Most clinical trials call for the use of the best available donor when a BMT is required. An HLA-identical sibling is usually the most preferred source, but many patients will not have this option as each sibling has only a 25% chance of being an HLA match. When an HLA-identical sibling is not available, the decision of what donor source to use varies among transplant centers. Each source has its own advantages and disadvantages, and further clinical trials are needed in this area.

Supportive care is extremely important in the treatment of children with AML because the therapy can be very toxic and myelosuppressive, causing long periods of transfusion dependence and severe neutropenia. Most patients are kept in the hospital during their initial induction therapy until recovery of the absolute neutrophil count. Risk of infection is the most problematic toxicity in AML treatment, and watching patients closely in the hospital allows for prevention and prompt intervention in the event of fever or signs of sepsis. A patient with AML who presents with fever and neutropenia should be considered a medical emergency. Appropriate blood cultures should be drawn and broad spectrum intravenous antibiotics immediately started. These antibiotics should include a third- or fourth-generation cephalosporin (ceftazidime or cefepime) with vancomycin. Vancomycin is active against the organism streptococcal viridans. This organism can cause severe sepsis and death in patients who have received AML-directed chemotherapy, especially those receiving high-dose cytarabine. Invasive fungal infections are also a problem in AML and should be considered in patients who are persistently febrile despite broad spectrum antibiotic drug use. Appropriately diagnosing fungal disease can be a challenge, and early consultation with pediatric infectious disease is very important. Many patients will require computed tomography, bronchoscopy, or biopsy of suspicious lesions for definitive diagnosis and treatment planning. The use of antifungal prophylaxis can benefit patients with AML, (19) and antibacterial prophylaxis can also be used. (20) Antibacterial and antifungal prophylaxis regimens used by individual institutions vary.

Down syndrome–associated AML has its own unique biological and prognostic characteristics. Overall, patients with Down syndrome have an 80% EFS because the leukemia tends to be more sensitive to cytarabine and daunorubicin. (21) This survival advantage can be accomplished with less intensive chemotherapy. This is very important because children with Down syndrome are at increased risk for therapy-related toxicity. Recent clinical trials have successfully reduced therapy burden with reduction in anthracycline use, high-dose cytarabine, and CNS-directed therapy. (22) As in other patients with AML, supportive care is extremely important in this patient population.

Relapsed AML continues to be a therapeutic challenge with a very poor prognosis. Many patients with relapsed disease can be difficult to induce remission or make MRD negative. This makes BMT impossible or less effective. The chemotherapy used in these patients is very toxic, with significant short- and long-term risks. Patients who relapse after BMT have an extremely poor prognosis and have limited therapeutic options. Future clinical trials are needed for this group of patients using more targeted therapies. Unfortunately, this field has not grown nearly to the same degree seen in ALL.

Chronic Myelogenous Leukemia

CML was the first malignancy linked to a specific genetic translocation causing uncontrolled proliferation of myeloid cells, including varied stages of granulocytes, red blood cells, and platelets. The disease can develop slowly with a very long prodrome before diagnosis. This very distinctive disease can cause extremely high WBC counts along with thrombocytosis. Although CML makes up a very small percentage of childhood leukemia, its unique presentation, molecular characteristics, and therapeutic advances are fascinating. CML presents more commonly in adolescence but can occur at any age. Its morphologic characteristics are unique, with an elevated WBC count, neutrophilia, increased metamyelocytes and myelocytes, eosinophilia, basophilia, and thrombocytosis. The t(9;22) translocation, or Ph, and the resulting fusion gene *BCR-ABL* are pathognomonic of the disease and are required to make the diagnosis. This can be accomplished using peripheral blood, making the diagnosis relatively uncomplicated. Children and adolescents present similarly to adults with signs and symptoms related to extremely high WBC counts and sometimes massive hepatosplenomegaly. Patients can be asymptomatic or have fatigue, fever, night sweats, weight loss, abdominal distention, or mood disturbance.

Treatment of CML has been revolutionized with the development of TKIs. This class of medication targets enzymes that are responsible for cell growth and division. In CML the Bcr-Abl tyrosine kinase is responsible for abnormal cell growth because it has abnormally increased activity. The TKIs imatinib and dasatinib are potent inhibitors of this tyrosine kinase. Historically, the outlook for these patients was poor, with BMT being the only curative treatment. TKIs allow for excellent disease control with relatively minimal toxicity. In children, the current standard of care is to begin imatinib or dasatinib at diagnosis. Even in patients who have an HLA-matched sibling, BMT is reserved only for the rare cases where the disease becomes resistant to TKI therapy. The challenge going forward is to decide how long patients need to remain on TKI therapy. The long-term toxicity associated with using these medications also needs to be explored. There are current ongoing trials in adults evaluating groups of patients who can be taken off TKIs after many years of therapy. This needs further research in children.

LATE EFFECTS OF THERAPY

The long-term complications of leukemia treatment vary widely by diagnosis and regimen. The late effects seen in a patient with standard-risk ALL are very different than those experienced by a patient with AML who required a BMT. Many pediatric oncology centers now have programs dedicated to survivorship. These multidisciplinary clinics include physicians, advanced care practitioners, dietitians, psychologists, social workers, school counselors, and easy access to other pediatric specialties. Survivors of childhood leukemia should be followed in these clinics yearly. These clinics are a conduit to primary care pediatricians and provide tailored outlines of potential long-term complications with required follow-up and screening.

Standard-risk patients with ALL have relatively few long-term complications. Most of these are related to the neuropsychological consequences of intrathecal methotrexate. Past studies evaluating the neurocognitive effect of treatment included those that received cranial radiation, thereby making extrapolating possible outcomes for today's survivors difficult. Survivors of childhood ALL have problems with processing speed, attention, and impaired executive functioning. These changes can be subtle in many cases and require formal neuropsychological testing to be found. This testing should be performed if the patient has problems in school or before a change in academic rigor. In general, patients should have testing before entering kindergarten, middle school, high school, and college. This will allow for interventions before problems start, and educational strategies can be tailored to the individual student's strengths and weaknesses.

Osteonecrosis is a very common adverse effect of contemporary ALL therapy. This complication can have significant effects on quality of life by causing arthritis, difficulties with activities of daily living, pain, and reduced range of motion. Adolescents are much more likely to be affected by osteonecrosis, and it can be seen in up to 20% of this age group. (23) Corticosteroids, particularly dexamethasone, are the major cause of this problem. Corticosteroids cause marrow fat cell hypertrophy and elevated intraosseous pressure. This leads to decreased blood flow and eventual marrow and bone necrosis. Host factors also may play a role. (24) The knees, hips, shoulders, and ankles can all be affected. Treatment is generally supportive, with some patients requiring arthroplasty when the disease is severe.

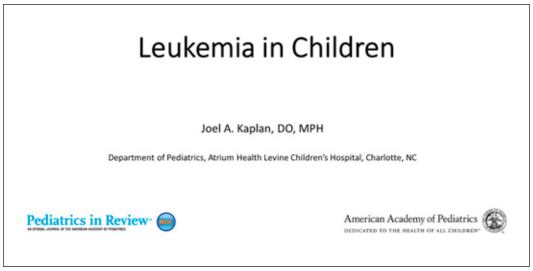
Long-term cardiac toxicity is a concern in patients with leukemia secondary to the use of anthracyclines. The risk of cardiotoxicity is directly related to the total dose used. The cumulative dose of anthracyclines used in ALL is very low, as is the risk of long-term cardiac toxicity. (25) However, there may not be a truly safe dose of anthracycline because small structural changes in the heart can be found, albeit with questionable clinical significance, even in those receiving lower doses. (26) AML therapy incorporates the use of both daunorubicin and mitoxantrone, both members of the anthracycline class. Patients with AML require much larger doses of anthracyclines compared with those with ALL. These patients require yearly echocardiograms to screen for cardiomyopathy and heart strain. If an abnormality is found, prompt referral to a pediatric cardiologist is warranted. Dexrazoxane is a cardioprotective agent that can be used in patients with AML to reduce the risk of future cardiomyopathy, but its use is not universal. There is evidence that this agent decreases the long-term risk of cardiomyopathy in those receiving higher doses of anthracyclines. (27)

Other late effects, including obesity, the associated metabolic syndrome, endocrine abnormalities, secondary malignancies, and growth disturbances, have been found in patients with leukemia. These are much more common in patients who received a BMT or cranial radiation. Infertility is uncommon in most patients with AML or ALL who did not receive a BMT. However, all patients at diagnosis should be counseled and offered sperm banking and egg harvesting or ovarian cryopreservation if appropriate.

Summary

- Based on strong research evidence (level A) in the form of numerous phase 3 clinical trials and clinical observation, childhood leukemia presents with signs and symptoms of cytopenias, fever, bone pain, limp, and refusal to walk. Patients may also have hepatosplenomegaly and symptoms related to central nervous system disease.
- Based on strong research evidence (level A) in the form of clinical observations and clinical studies, hyperleukocytosis should be treated immediately with appropriate supportive care. In most patients the use of leukapheresis can be avoided. (6)
- Based on strong research evidence (level A) in the form of multiple phase 3 clinical trials, acute lymphoblastic leukemia (ALL) in children has an excellent prognosis. T-cell disease now has a similar prognosis to B-cell disease. The event-free survival varies among different ALL subgroups, and therapy should be tailored accordingly. (7)(10)
- Based on strong research evidence (level A) in the form of phase 3 clinical trials, patients with trisomy 21 and acute myelogenous leukemia (AML) have a favorable prognosis. (15)
- Based on strong research evidence (level A) in the form of multiple phase 3 clinical trials, minimal residual disease testing has prognostic significance across ALL and its subgroups and AML. (7)(8) Phase 3 clinical trials compare the existing standard of care treatment with a new treatment called the experimental arm of the study. The experimental arm can be used to test the effectiveness of a new drug, dose, or schedule. Many phase 3 pediatric oncology trials are accomplished with a large number of patients using the cooperative group model.
- Based on strong research evidence (level A) in the form of clinical trials, Philadelphia chromosome–positive ALL has much improved outcomes with the use of tyrosine kinase inhibitors. (11)
- Based on strong research evidence (level A) in the form of clinical research and clinical guidelines, supportive care is extremely important in patients with AML. Special attention should be given to fever and the development of streptococcal viridans sepsis.
- Based on strong research evidence (level A), the targeted immunotherapies blinatumamab, chimeric antigen receptor T-cell therapy, and inotuzumab show excellent results for relapsed patients with ALL. (13)(14)(15)(16)(17)

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/40/7/319.supplemental.**



Leukemia in Children

Joel A. Kaplan, DO, MPH

Department of Pediatrics, Atrium Health Levine Children's Hospital, Charlotte, NC

References for this article are at http://pedsinreview.aappublications.org/content/40/7/319.

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1. A 3-year-old boy is brought to the office with complaints of fever and pain in the legs. The fever has been intermittent and as high as 101.5°F (38.6°C) for the past 5 days, and the pain in the legs is waking him up at night. He has a negative medical history, and his immunizations are up-to-date. The mother noted that he has had some bruising on the arms and legs, but she accounts for that by his active play. He had a viral infection approximately 3 weeks ago that resolved without treatment. Vital signs include a temperature of 100.8°F (38.2°C), a heart rate of 120 beats/min, a respiratory rate of 24 breaths/min, blood pressure of 100/60 mm Hg, and oxygen saturation of 100% on room air. There is mild cervical lymphadenopathy, and results of the heart and lung examinations are normal. The abdomen is soft, without hepatosplenomegaly. The extremities show mild discomfort, with scattered ecchymoses. Neurologic examination findings are normal. Laboratory studies show a white blood cell (WBC) count of 1,500/μL (1.5×10^9/L), a hemoglobin level of 8.5 g/dL (85 g/L), a hematocrit value of 24%, a platelet count of $75\times10^3/\mu$L (75×10^9/L), a reticulocyte count of 0.4%, and a differential count of 5% neutrophils, 85% lymphocytes, 5% eosinophils, and 5% monocytes. Which of the following is the most likely diagnosis in this patient?
   - A. Acute lymphocytic leukemia.
   - B. Aplastic anemia.
   - C. Chronic lymphocytic leukemia.
   - D. Infectious mononucleosis.
   - E. Viral suppression.
2. A 14-year-old girl is brought to the emergency department with a history of fatigue, pallor, and bruising. On physical examination the vital signs show a temperature of 100.0°F (37.8°C), a heart rate of 100 beats/min, a respiratory rate of 20 breaths/min, and BP of 110/65 mm Hg. Physical examination shows a pale adolescent in no acute distress. There is mild cervical adenopathy, and the lungs are clear. A grade 2/6 systolic murmur is heard. The abdomen is soft, with the spleen palpable 3 cm below the left costal margin. The liver is 1 cm below the right costal margin. Neurologic examination findings are normal. Extremities show scattered bruising. Laboratory data show a WBC count of 150,000/μL (150×10^9/L); a hemoglobin level of 6 g/dL (60 g/L); a hematocrit value of 18%; a platelet count of 10×10^3 /μL (10×10^9/L); a differential count of 95% atypical lymphocytes, 2% monocytes, and 3% neutrophils; a blood urea nitrogen level of 10 mg/dL (3.6 mmol/L); a creatinine level of 0.5 mg/dL (44.2 μmol/L); and a potassium level of 3.0 mEq/L (3.0 mmol/L). The patient is admitted to the hospital, and flow cytometry on a bone marrow aspirate shows pre–B-cell acute lymphocytic leukemia. The girl begins chemotherapy with vincristine, doxorubicin, and prednisone, with planned L-asparaginase on day 4 of therapy. Twenty-four hours after beginning therapy the nurse calls and says that the patient has not urinated in 8 hours. The blood pressure is now 140/90 mm Hg. Laboratory data show a blood urea nitrogen level of 30 mg/dL (10.7 mmol/L), a creatinine level of 2.5 mg/dL (221.0 μmol/L), a phosphorus level of 6 mg/dL (1.9 mmol/L), a calcium level of 7.5 mg/dL (1.9 mmol/L), a lipase level of 100 U/L (1.7 μkat/L), and a potassium level of 5.0 mEq/L (5.0 mmol/L). Which of the following is the most likely explanation for the change in the patient's status and laboratory data?
   - A. Cardiac failure.
   - B. Dehydration.
   - C. Gastrointestinal bleeding.
   - D. Pancreatitis.
   - E. Tumor lysis syndrome.

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3. As treatment is continued, the treating physician discusses the diagnosis with the parents, who ask about the prognosis and treatment for their child. Which of the following is the most appropriate response to the family?
    - A. High risk and will require a bone marrow transplant.
    - B. High risk and will require chemotherapy.
    - C. High risk and will require treatment with tyrosine kinase inhibitors.
    - D. Low risk and will require a bone marrow transplant.
    - E. Standard risk and will require chemotherapy.
4. A 16-year-old boy is brought to the emergency department for complaints of fatigue and abdominal fullness. He has had intermittent fever to 101.0°F (38.3°C) for the past week but has been continuing to go to school. His physical examination shows a pale adolescent in no acute distress. His temperature is 99.5°F (37.5°C), heart rate is 90 beats/min, respiratory rate is 18 breaths/min, and blood pressure is 110/70 mm Hg. Heart and lung examination findings are normal, and the abdomen shows the spleen to be palpable 4 cm below the left costal margin. Neurologic examination findings are normal. The skin shows facial acne. Laboratory data show a WBC count of 150,000/μL (150×10^9/L), a hemoglobin level of 10 g/dL (100 g/L), a hematocrit value of 28%, a platelet count of $400 \times 10^3/\mu$L (400×10^9/L), and a differential count of 3% blasts, 8% myelocytes, 10% metamyelocytes, 20% bands, 40% neutrophils, 5% basophils, and 14% lymphocytes. Which of the following is the most likely chromosomal abnormality to be seen in this patient?
    - A. t(8;21).
    - B. t(9;22).
    - C. 11q23.
    - D. t(15;17).
    - E. Trisomy 21.
5. A 15-year-old boy is brought to the office for routine health care maintenance. He has been generally doing well, but his medical history is significant for acute myelogenous leukemia treated with cytarabine, daunorubicin, etoposide, and mitoxantrone. He has been off therapy and in continuous remission for 7 years and is doing well in school. His physical examination shows no abnormalities. He is Tanner stage 4. Which of the following is the most appropriate test to perform in this patient?
    - A. Echocardiography.
    - B. Hearing evaluation.
    - C. Hemoglobin A1c.
    - D. Serum follicle-stimulating hormone, luteinizing hormone, and testosterone.
    - E. Radiographs of the hips.

Leukemia in Children

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Acute Ataxia in Children

Philip Overby, MD, MA,*† Matthew Kapklein, MD,† Ronald I. Jacobson, MD*†

**Department of Neurology and †Department of Pediatrics, New York Medical College, Valhalla, NY*

Practice Gaps

The word *ataxia* in medicine frequently is used to signify not only difficulty walking but also difficulty walking specifically due to cerebellar dysfunction. However, although gait and cerebellar disorders can overlap, they are not synonymous. The purpose of this review is to illustrate how children with difficulty walking present, which includes, but is not limited to, patients with cerebellar disorders. In addition, the goal is to illustrate both the more common and the more urgent causes of acute ataxia in children.

Objectives

After completing this article, readers should be able to:

1. Recognize the most common and the most urgent causes of acute ataxia in children.
2. Recognize that ataxia is a nonlocalizing complaint, frequently misinterpreted as being localized entirely to the cerebellum.
3. Take the first steps in the evaluation and management of acute ataxia.

Acute ataxia is fairly common in children. The most common cause, acute cerebellar ataxia (ACA), is estimated to occur in 1 in 100,000 children. (5) The causes of acute ataxia in children are typically benign but at times can represent serious illness. The comprehensive range of potential causes is broad, but typical causes are few and have changed in the post–varicella vaccine era. Ataxia is also frequently thought to represent cerebellar disease but can, in fact, be due to dysfunction of any part of the nervous system or occasionally nonneurologic mechanisms. This paper reviews the common causes of acute ataxia in children, as well as less common causes that should not be missed. It attempts to aid the reader in approaching the neurologic examination, as well as the first steps in the management of the ataxic child.

Ataxia derives from the Greek—*a* (without), *taktos* (order)—and means a lack of order. Broadly, ataxia encompasses disorders in which there is an absence of coordinated motor movements, often involving gait; however, gait disorders can also present with dysfunction not due to cerebellar dysfunction. Both can rightly be called ataxia. In other words, ataxia is a nonlocalizing complaint. It can emerge from disorders affecting the brain through the spinal cord, as well as peripherally from nerves to muscles. Attempting to localize the

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ABBREVIATIONS

ACA	acute cerebellar ataxia
ADEM	acute disseminated encephalomyelitis
CSF	cerebrospinal fluid
CT	computed tomographic
GBS	Guillain-Barre syndrome
ICH	intracerebral hemorrhage
ICP	intracranial pressure
IV	intravenous
IVIg	intravenous immunoglobulin
MRI	magnetic resonance imaging
NMDA	*N*-methyl-D-aspartate
OMS	opsoclonus-myoclonus syndrome
TM	transverse myelitis
tPA	tissue plasminogen activator
WBC	white blood cell

source of dysfunction should guide the history, examination, and subsequent studies. As such, the history and examination should be directed at determining whether the patient has a disorder of coordinated movements, ie, cerebellar dysfunction, or is struggling to walk due to other causes.

Although ataxia can certainly be chronic, subacute, or intermittent, it is usually acute as a presenting symptom in children. This review focuses primarily on acute ataxia, typically defined as ataxia for less than 72 hours, with particular attention to specific diagnoses and relevant diagnostic testing. For the treating physician, the list of its potential causes can be daunting, (1) in part because ataxia can by caused by dysfunction at any level of the motor system, from brain to muscle (Table 1). It can even be due to sensory impairment. Diagnostically, the goal is to localize the ataxia to the level of dysfunction. Practically, the initial approach to the child with acute ataxia should focus on the serious causes of ataxia. Once these have been excluded clinically, more common as well as treatable causes can be considered. Life-threatening conditions fall into 4 broad categories: infection and/or inflammation, neoplasm, stroke, and ingestion. This review discusses the initial steps when approaching the patient with acute ataxia, followed by a limited discussion of management.

HISTORY

Although the initial history should be directed foremost at identifying serious causes of acute ataxia, in most patients the causes of acute ataxia are self-limited and benign. One retrospective study of 40 pediatric cases found that 80% could be attributed to ACA, toxic ingestion, and Guillain-Barre syndrome (GBS). (6) The history should explore evidence of recent or current infection: fever, rash, respiratory symptoms, or vomiting. Questions about possible toxic exposures in the home, such as medications, alcohol, or illicit drugs, are essential. The possibility of trauma, observed or potentially unobserved, should be explored with all caregivers and children who might be aware of it.

Associated symptoms can further guide the history. For example, although ACA is characterized by preservation of alertness, a change in mental status is concerning and can signal a systemic process, brain tumor, or cerebellitis. Headaches, recurrent vomiting, vision loss or diplopia, and worsening of symptoms when supine can be signs of elevated intracranial pressure (ICP) from hydrocephalus in the setting of posterior fossa masses. Note, however, that these findings can be late or even intermittent, and their absence does not exclude elevated ICP from any cause. Considerations involving ataxia with altered mental status include toxic ingestion, infection, or mechanical compression of the brain stem by a tumor or abscess. Recent and abrupt onset of symptoms is more suggestive of a vascular, toxic, or infectious cause. Tumors and immune-mediated processes are typically more subacute in their progression. Previous similar episodes are suggestive of chronic conditions such as migraine, vestibular dysfunction, or even seizures. Recurrent episodes are also potentially suggestive of metabolic processes (Table 1).

Life-threatening causes of acute ataxia typically originate in the central nervous system. Altered mental status, vomiting, or visual disturbances in the presence of ataxia are red flags. Life-threatening causes typically involve the posterior fossa and/or brain stem. In particular, symptoms refer to 3 sources: the cranial nerves, the pyramidal tracts, and the cerebellum. Moreover, the involvement of brainstem and cerebellar structures typically results in abnormalities on both history and physical examination. As such, a normal neurologic examination, carefully performed, is a pertinent negative.

PHYSICAL EXAMINATION

The physical examination begins with vital signs. Fever suggests infection. Hypertension is nonspecific but can be caused by elevated ICP, eg, in ischemic or hemorrhagic stroke or acute hydrocephalus. Elevated BP and/or tachycardia can also occur with peripheral processes such as GBS.

GENERAL EXAMINATION

Initial observations (eg, Does the child appear ill or uncomfortable? Is he or she agitated or taking care not to move?) are valuable. The examination can be challenging because the child may be uncooperative. Given this, the examination should move from the least to the most invasive.

The somatic examination should explore for evidence of meningismus: neck stiffness with flexion and photophobia and discomfort with extraocular movement. On occasion, acute ataxia or vertiginous gait may be caused by acute otitis media. Otitis media, tender red mastoid, or mastoid bruits suggest infectious mechanisms, vestibular disorders, or venous occlusive disorders. Any process causing lower extremity or back pain may produce a gait disturbance termed *antalgic gait*. Careful inspection of toes, nails, foot structure, and all lower extremity joints, in addition to back spasm, scoliosis, and spinal deformities, may reveal that the cause of gait dysfunction is from antalgic gait even without the complaint of pain, particularly in younger children.

TABLE 1. Selected Causes of Acute Ataxia in Childhood

INFECTIOUS OR PARAINFECTIOUS	VASCULAR	GENETIC/METABOLIC
Acute cerebellar ataxia	Arteriovenous malformation	Abetalipoproteinemia
Acute cerebellitis	Vasculitis	Arginosuccinic aciduria
Opsoclonus-myoclonus ataxia	Ischemic stroke	Vitamin E deficiency
Transverse myelitis	Intracerebral hemorrhage	GM2 gangliosidosis
Guillain-Barre syndrome		Hartnup disease
Coxsackievirus	**TOXIC**	Hyperalaninemia
Echovirus	Alcohol	Hyperammonemia
Epstein-Barr virus	Lead encephalopathy	Hypoglycemia
Mumps encephalitis	Benzodiazepines	Kearns-Sayre syndrome
Japanese B encephalitis	Opioids	Leigh disease
Mycoplasma pneumoniae	Antihistamines	Maple syrup urine disease
Pertussis		Myoclonic epilepsy with ragged red fibers
Polio		Metachromatic leukodystrophy
Enterovirus D68	**TRAUMATIC**	Adrenoleukodystrophy
Tuberculosis	Acute cerebellar edema	Mitochondrial complex defects
Varicella virus		Biotinidase deficiency
Borrelia burgdorferi	**PSYCHOGENIC**	Neuronal ceroid lipofuscinosis
Powassan virus	Conversion reaction/functional	Sialidosis
NEOPLASTIC		Niemann-Pick disease
Cerebellar or frontal tumors	**MISCELLANEOUS**	Refsum disease
Neuroblastoma	Hydrocephalus/shunt dysfunction	Neuropathy, ataxia, retinitis pigmentosa
Pontine tumors	Complex migraine	Wernicke encephalopathy
Spinal cord tumors		Tryptophanuria
		Triosephosphate isomerase deficiency

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Pupil abnormalities suggest many etiologies, such as toxins and drugs (large from atropinergic agents or small from opiates) or third nerve compression resulting in ptosis, enlarged pupil, and ocular abduction. Torticollis, head tilt, or any resistance to neck motion suggests a craniocervical junction disorder such as Chiari malformation, cervical cord compression, or posterior fossa tumors. Impairment of extraocular movement from a pontine glioma, medulloblastoma, or cerebellar astrocytoma may cause a head tilt without restriction of head/neck range of motion. Acute gait disorders may be nonneurologic and caused by psychogenic mechanisms. The analysis of nonneurologic gait disorders is complex and is discussed separately in this review.

NEUROLOGIC EXAMINATION

Neurologic evaluation begins with the child's mental status. Behavioral changes, decreased alertness, inattention, or dysarthria can all be clues to elevated ICP, brainstem compression, or cranial neuropathies that may affect eye movements. Fundi should be inspected for papilledema. Evaluating for disc blurring can be difficult; sometimes the presence or absence of venous pulsations is more evident. The absence of venous pulsations can be due to elevated ICP. The presence or absence of further associated findings to suggest elevated ICP, such as restriction of upward gaze or lateral eye movements, should also be noted.

Initially it is ideal to observe a child's gait in a natural setting, such as while walking into the examination room or office. To reduce artificial or unnatural gait patterns induced by intense observation or merely the request to walk, it is useful to throw a ball and ask the patient to both walk then run to pick up the ball. Ataxia and other gait disturbances may be best revealed as the patient turns to walk back. Patients with narrow-based gait are unlikely to have cerebellar pathway diseases.

Cerebellar hemisphere dysfunction is often associated with a wide-based gait. Forms of identifiable cerebellar dysfunction discernible on examination are manifold. Cerebellar ataxia includes abasia (unsteady stance), dysmetria (impaired excursions in movement), dysdiadochokinesis (nonrhythmic and impaired alternating movements), dyssynergia (decomposition of movement into sequential tasks), or truncal ataxia if the cerebellar vermis is involved.

However, ataxia—understood as a gait disorder—can also refer to the cranial nerves or motor or sensory impairments. In cooperative patients one should first evaluate for dysmetria in each upper extremity. If the index finger misses the target it may be from cerebellar dysfunction, weakness, or impaired vision. To distinguish among these, one should first look for dysdiadochokinesis—a cerebellar finding. Alternatively, diplopia can cause patients to miss the target. Covering 1 eye of the patient typically eliminates diplopia. In patients with diplopia, each eye and its movements should be evaluated individually. The presence of ptosis is most commonly due to Horner syndrome or third nerve palsy. To identify limb weakness, one should have the patient extend both arms out horizontal to the floor "as if holding a pizza tray." The presence of drift, ie, gradual lowering of one arm, suggests ipsilateral arm weakness, and a full motor examination is necessary. Unilateral weakness or pyramidal tract dysfunction manifests as asymmetries in arm or leg use. Subtle gait difficulties can be elicited with tandem walking or running; impaired arm swing suggests ipsilateral weakness

A lurching gait or falling to one side is typical with vestibular dysfunction (often confused for cerebellar dysfunction in young children who cannot describe the subjective experience of vertigo). Sudden lurching or falling to one side triggered by head rotation suggests vestibular dysfunction.

Sensory ataxia also causes a positive Romberg test, which examines the dorsal columns. Attempts to stand with feet close together can result in swaying from side to side with eyes open or closed (termed a positive Romberg test when the eyes are closed). A positive test is one in which swaying or a frank fall occurs. Young children with acute lower extremity weakness from GBS or myositis may manifest ataxia and falling, a gait disturbance termed *pseudo-ataxia*. Muscle stretch reflexes can provide essential information but can also mislead the examiner. Evaluation for presence or absence is particularly important when there is suspicion for GBS. More generally, however, asymmetrical reflexes and the presence or absence of upgoing toes (the latter an upper motor neuron sign) can be misleading. These findings should be interpreted cautiously and used as supportive evidence of suspected underlying central or peripheral processes, prompting further evidence of motor or sensory impairments. For example, asymmetrical brisk reflexes alone may be pathologic or may be an artifact of patient positioning, and exaggerated reflexes with ipsilateral atrophy and weakness suggest chronic corticospinal involvement.

DIFFERENTIAL DIAGNOSIS

There are 2 intersecting axes to draw from the history and examination: localization of the disorder and pathology. When first evaluating a patient, the tempo of presentation can provide clues to pathology. For example, infection and immune-mediated disorders are typically acute to subacute and frequently affect multiple systems. Ischemic strokes typically present with maximal deficit and an acute onset, whereas complex migraines evolve over 15 to 30 minutes. Brain tumors are chronic but can present acutely in the presence of acute hemorrhage, cerebrospinal fluid (CSF) obstruction, or seizure.

The potential causes are listed in the following subsections in an order attempting to synthesize a combination of both most urgent and most likely diagnoses. Strokes are uncommon but urgent; migraines are common but not urgent. Immune-mediated processes are very common and potentially urgent. Table 2 lists the relative frequency of etiologies for acute ataxia.

Vascular

Stroke is the most urgent, if not the most likely, consideration. Hemorrhagic stroke, ie, acute intracerebral hemorrhage (ICH), is a neurologic emergency. Large hemorrhages causing mass effect or cerebellar hemorrhages threatening the brain stem require urgent neurosurgical evaluation and treatment. The most common cause of spontaneous ICH in children is arteriovenous malformation. (2) A noncontrast head computed tomographic (CT) scan is the best initial diagnostic test for ICH, performed urgently.

Ischemic strokes can also cause ataxia. Ideal imaging (CT vs magnetic resonance imaging [MRI]) should be discussed urgently with a neurology consult based on time of presentation and degree of clinical suspicion for stroke. With all ischemic strokes, the first question to ask is, "Can tissue plasminogen activator (tPA) be given?" tPA is a thrombolytic therapy for ischemic stroke. It can be given systemically intravenously (IV) for ischemic strokes in patients seen less than 4.5 hours after onset. After this time, efficacy decreases and there is higher risk of cerebral hemorrhage. tPA can also be given intra-arterially by interventional neuroradiologists. Intra-arterial tPA can be given up to 6 hours after onset. tPA is most commonly given for adults but is used increasingly in pediatric patients. (3)

The level of evidence in children for tPA is limited to expert opinion. Its use is off-label in children and limited to certain pediatric stroke centers; however, if the clinical presentation is suggestive of an ischemic stroke, urgent transfer to a pediatric stroke center should be considered.

Trauma

Life-threatening conditions to consider in the setting of trauma are hemorrhagic stroke resulting in contusion(s) and ischemic stroke from arterial dissection. In the absence of more diffuse axonal injury causing associated encephalopathy, it is unusual for trauma to present with isolated ataxia. The important exception to this rule is arterial dissection, which represents 5% to 25% of pediatric ischemic strokes. The vertebral arteries supply the posterior circulation and cerebellum. Presenting signs and symptoms refer to the posterior fossa: ataxia, vertigo, vomiting, diplopia, and head and neck pain. Although these symptoms are common and nonspecific, 88% of patients in a recent review had focal neurologic deficits. (3) Fifty percent of children in the same study had a history of trauma. Cerebral concussion may cause vertigo, gait disturbance, and a positive Romberg test, often termed *vestibular concussion,* and it is frequently underdiagnosed in our experience.

Toxic Ingestion

Ingestion of a toxin represents a major cause of ataxia in children, accounting for approximately 10% (7) and up to one-third (4) of cases. Sending a urine sample to toxicology, particularly in children younger than 5 years, is a high-yield and efficient practice. In our experience, the most common presentation of toxin ingestion is a combination of ataxia and somnolence without antecedent illness. In addition, there can be a discrepancy between the high degree of unresponsiveness and patients' otherwise overall benign appearance. After ingestion, patients can simply appear to be sleeping. Vital signs are often normal. Although urine toxicology screens do not identify many prescription medications, they do identify the most urgent: benzodiazepines and opioids, which can impair respiration. Accidental ingestion occurs in young children. Adolescents can also present after ingestion in attempts to self-harm. Symptoms of ingestion can be nonspecific. Indeed, when symptoms do not fit well into a clinical syndrome, and

TABLE 2. **Acute Ataxia Etiologies**

ETIOLOGY	PATIENTS, NO. (%) (N = 120)
Postinfectious cerebellar ataxia	71(59.2)
Drug intoxication	10 (8.3)
Opsoclonus-myoclonus ataxia	10 (8.3)
Acute cerebellitis	3 (2.5)
Cerebellar stroke	2 (1.7)
Acute disseminated encephalomyelitis	2 (1.7)
Meningitis	1 (0.8)
Cerebral vein thrombosis	1 (0.8)
Miller Fisher syndrome	1 (0.8)
Concussion	1 (0.8)
Genetic (first episode of episodic ataxia (n = 5), Leigh syndrome (n = 1), undiagnosed (n = 1)	7 (5.8)
Idiopathic	11 (9.2)

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when these symptoms spontaneously improve within 12 to 24 hours, ingestion should become a concern. A thorough history of medications in the home(s) or child care is essential. When considering toxic ingestion, it is also important to evaluate for other evidence of metabolic aberrations, such as hypoglycemia, hyponatremia, and hyperammonemia.

Immune-Mediated/Postinfectious Causes

ACA, Cerebellitis, Opsoclonus-Myoclonus Syndrome. ACA is the most common cause of acute ataxia in children. It is a benign, typically postinfectious or parainfectious phenomenon. Presentation is fairly characteristic, but it needs to be distinguished from more worrisome causes of ataxia that can initially look similar, namely, opsoclonus-myoclonus syndrome (OMS) or cerebellitis.

ACA typically occurs in preschool- and school-aged children. Generally, the acute ataxia is most prominent on awakening and improves over the course of days to weeks or, rarely, months. Nystagmus is uncommon. Truncal ataxia with trouble sitting and appendicular intention tremor are typical findings. Children are afebrile, alert, and well-appearing.

Acute cerebellitis is likely the extreme end of a continuous clinical phenomenon, with ACA representing the milder end. Clinically, patients with cerebellitis appear more ill than those with ACA. Patients with cerebellitis have ataxia as well as further symptoms, such as vomiting, altered mental status, increased sedation, or seizures and abnormal brain imaging findings. Numerous case reports of fulminant presentations with varying outcomes have been reported. (5) Initial presentation can be fulminant or subacute. Unlike its more benign form, fulminant cerebellitis progresses from its onset to the development of encephalopathy, with hydrocephalus caused by obstruction of the fourth ventricle. Unlike ACA, outcomes of cerebellitis are not always favorable but can potentially be improved with aggressive management: typically, CSF diversion and/or corticosteroids with supportive ICU care.

Connolly et al (6) described a cohort of 73 patients with ACA in 1994. This study predates wide adoption of the varicella vaccine. In 78% of these patients, a preceding viral illness was identified (19 patients with varicella and 2 with Epstein-Barr virus). Two cases were associated with vaccines, and the rest were idiopathic. The latency of known precipitant to onset was 1 to 43 days. On follow-up, at least 90% of patients had made a full recovery.

A more recent cohort (Table 2) of pediatric patients presenting with ataxia was published in 2016. (7) This was a retrospective review of all patients (N = 120) presenting with ataxia to Children's Hospital of Pittsburgh from 2003 through 2013. Of patients with acute ataxia, 82% were 1 to 6 years old and 16% were 6 years or older, with an overall age range of 6 months to 18 years.

Of this cohort, 71 patients (59%) had ACA; 85% of patients with ACA were 1 to 6 years old, 15% were older than 6 years, and none were younger than 1 year. Mean time to presentation was 8.2 days. In this post–varicella vaccine era study, none of the patients had varicella. Only 2 cases were attributed to vaccines. Of the 71 patients, 58 had a lumbar puncture, of whom 40% had a CSF pleocytosis (range, 6–60 cells/mm^3). In addition, many patients were tested for varicella, Epstein-Barr virus, herpes simplex virus, cytomegalovirus, and enterovirus by CSF polymerase chain reaction; all were negative. Finally, brain MRI was performed in 69 of 71 patients, and all the results were normal.

In follow-up, 91% of patients had recovered by 30 days, the remainder by 6 months. Three patients received intravenous immunoglobulin (IVIg), with recovery at 2 to 4 months. Three patients received corticosteroids, with recovery at 2 to 4 weeks. Indications for immune-modulating therapy were not discussed.

Cerebellitis was found in 3 of the 120 patients. All 3 patients had concurrent viral respiratory infections; 1 required decompressive craniotomy. These patients were aged 16 months to 8 years. Vomiting and headache were present in the 6- and 8-year-olds. All the patients "appeared ill," had an elevated white blood cell (WBC) count or protein level in the CSF, and had abnormal findings on brain MRI, with signal hyperintensities in the cerebellum. One patient had recovered at 3-month follow-up, the 16-month-old had cognitive difficulties and ataxia at 3-month follow-up, and the third patient was lost to follow-up.

Of considerable interest is that in this cohort the number of patients presenting with ataxia due to OMS was the same as ingestion. Although this likely represents referral patterns to a large academic center, it also suggests that OMS may be more frequent than generally recognized, and this mirrors the authors' experience.

OMS is an immune-mediated, paraneoplastic encephalopathy seen most commonly in children younger than 4 years. (8) It has also been described as opsoclonus-myoclonus ataxia. Indeed, on initial presentation it may not be distinguishable from ACA. However, unlike ACA, patients with OMS both do not show rapid improvement and either present with or develop additional features, including developmental regression, feeding difficulties, irritability, sleep disturbance, and paroxysmal movements. Opsoclonus describes intrusive, rapid, saccadic eye movements. In the authors' experience, opsoclonus can be a late finding and, along with myoclonus, can be extremely brief and intermittent. Nevertheless, if a patient with suspected ACA is not improving as expected, is encephalopathic, or has paroxysmal limb or eye movements, it is essential to consider OMS. Once the diagnosis is made, the patient requires evaluation for occult neuroblastoma or ganglioneuroblastoma associated with OMS. Even when not identified, the presumption is that a small tumor with regression may have been present. Retrospective observational evidence suggests that aggressive immune therapy with a variety of agents, including but not limited to corticotropin, IVIg, and rituximab, has positive effects on the disordered immune response. (9)

Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating event that is typically most severe at onset. It is an immune-mediated encephalitis with or without myelitis often occurring in the context of viral or postviral infections. The white matter of the brain and spinal cord are preferentially affected. Typically, ADEM follows a prodrome of fever, vomiting, headache, and malaise. The neurologic features are broad: unilateral or bilateral pyramidal signs (60%–95%), acute hemiplegia (76%), ataxia (18%–65%), cranial nerve palsies (22%–45%), visual loss from optic neuritis (7%–23%), seizures (13%–35%), and spinal cord involvement (24%). (10) Current therapy, based on limited case reports and observational studies, is typically methylprednisolone, 10 to 30 mg/kg IV daily (maximum of 1 g daily), followed by a 4- to 6-week corticosteroid taper. (11) IVIg and plasmapheresis have also been used in refractory or recurrent cases. (12)(13) Although outcomes are typically good, there is emerging evidence of long-term effects, such as impaired brain growth (14) as well as subtle neurocognitive impairments in selected patients. (15)

Finally, more recent case series have identified novel causes for immune-mediated ataxia in childhood. Anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a common, autoimmune cause of encephalitis in children. NMDA receptor encephalitis was the most commonly identified cause of pediatric encephalitis in the California encephalitis project. (28) It was greater than 4 times more common than identified viral etiologies. NMDA receptor encephalitis has been identified in young patients (age <4 years) presenting with ataxia, followed by the more typical disturbances of sleep, autonomic dysfunction, encephalopathy, and sometimes seizures. (16) Paraneoplastic cerebellar degeneration due to voltage-gated P/Q-type calcium channel antibodies has also been described. (17)

Transverse Myelitis. Children with transverse myelitis (TM) may present with acute back pain associated with sensory or motor symptoms. (18) Urinary retention is common. Burning limb pain or sensory loss may be reported. Limb weakness is typical. Muscle stretch reflexes may be exaggerated or diminished. If the latter, distinguishing acute TM from GBS may be challenging. However, the presence of a sensory level and urinary retention are more suggestive of TM.

TM is an acute neurologic emergency. Urgent evaluation with MRI of the spine is required for TM and other potential myelopathic disorders, such as arteriovenous malformation with hemorrhage, epidural hematoma, or spinal cord tumor.

When TM is suspected, empirical treatment with corticosteroids should be considered. There is no clear evidence that corticosteroids worsen mimics of TM, such as spinal strokes, infections, or tumors. Retrospective data suggest improved outcomes in patients receiving corticosteroids early. (19) Therefore, a dose of methylprednisolone, 30 mg/kg per dose (maximum of 1,000 mg) IV, even as evaluation with imaging and lumbar puncture is underway, likely has rewards that outweigh the risks.

Labyrinthitis. The clinical symptoms of labyrinthitis are superficially similar to those of ACA: acute onset of ataxia, vertigo, and nystagmus. However, children with acute labyrinthitis generally appear more ill, have prominent vomiting, and hold themselves still to minimize exacerbation of symptoms. Nystagmus is the exception in ACA; it is typical with labyrinthitis. Movement worsens the vertigo. This condition frequently occurs in clusters of exposed individuals, most frequently in spring and early summer, supporting an infectious (likely viral) cause. In particular, the vestibular nerve is inflamed. In our experience, ACA is far more common in children younger than 5 years, and labyrinthitis is more common in children older than 5 years. A 2004 study of vestibular neuritis in adults found that vestibular function was improved in patients treated with methylprednisolone but not with valacyclovir. (20)

Guillain-Barre Syndrome. Studies of the incidence of GBS in children younger than 16 years, most of which have been performed in Europe and North America, suggest rates between 0.4 and 1.4 per 100,000. (21) Although the typical presentation of symmetrical weakness is well-known, an acute progressive ataxia is another presentation of GBS seen particularly in young children. Important early clues include distal paresthesia or numbness. Leg pain is not uncommon. Younger children may present with prominent symptoms of leg pain, agitation, or vomiting, and meningeal signs may be present on examination. Muscle stretch reflexes are depressed or absent but can be present on initial presentation. Lumbar puncture typically demonstrates dissociation between cells and protein, with elevated protein and borderline-to-normal WBC counts. The CSF may be normal on initial presentation. Three additional types of disorders need to be considered in the setting of suspected GBS. First, TM can also present with limb weakness, back pain, and depressed reflexes. Sustained urinary or bowel sphincter dysfunction and a sensory level distinguish TM from GBS. Second, tick paralysis can also present with pure motor weakness and absent reflexes. Particularly in the late spring or summer, if careful inspection reveals a tick, its removal is typically curative. Third, oculomotor paralysis can be a clue and can appear similar to the Miller Fisher variant of GBS, characterized by ataxia, oculomotor palsies, and absent deep tendon reflexes. Finally, brainstem encephalitis can also mimic the Miller Fisher variant of GBS.

Treatment is typically with IVIg, 0.4 g/kg IV daily for 5 days. A multicenter trial of 95 children suggested that treatment hastens recovery and decreases relapse but does not clearly affect overall outcome. (22)

Myasthenia Gravis. Myasthenia gravis presents with fluctuating pure motor weakness. Children may present with recent inability to walk that has since resolved but has been occurring repeatedly. Frequently there is evidence of concomitant ptosis or pharyngeal weakness. The fluctuating weakness can lead to falsely attributing weakness to a psychogenic cause. Therefore, examination should be directed toward evidence of fatigable weakness. Infectious illness can exacerbate myasthenic patients, causing them to present with acute weakness. Diagnosis is typically made using repetitive stimulation on electromyography/nerve conduction studies and with corroborating serum antibodies to synaptic antigens.

Infectious. During the prevaccine era, varicella was classically associated with ACA. In the post–varicella vaccine era, this is no longer the case. (23) However, beginning in 2014, enterovirus D68 emerged with a spike in incidence in children presenting with acute flaccid myelitis. In general, enterovirus D68 typically presents with respiratory or gastrointestinal illness in children and is most common in late summer to early fall. According to 1 retrospective review, approximately 20% of patients with acute flaccid myelitis require ICU care. (24) Acute flaccid myelitis most commonly occurs in children younger than 14 years, with a median age of 7 years, but it has been diagnosed in adults. (25) It follows the infectious prodrome and is characterized by flaccid paralysis involving 1 to 4 limbs. Weakness is commonly asymmetrical. Cranial neuropathies, particularly facial palsies, are common. Weakness develops over hours to days. Ataxia may not be the presenting complaint because upper limbs seem to be preferentially affected.

Pathologically, anterior horn cells and cranial nuclei are affected. MRI typically demonstrates longitudinally extensive, nonenhancing T2 signal change in the spinal cord. CSF typically demonstrates a mild pleocytosis (WBC count, $<100/\mu L$ [$<0.10\times10^9/L$]) and mild elevation in protein level. Virus can be identified from CSF, sputum, or stool. Empirical therapy with IVIg and/or corticosteroids has been ineffective in small cohort studies. (26)

Neoplastic

Childhood brain tumors occur most frequently in the posterior fossa. The most common tumors are medulloblastoma, brainstem glioma, ependymoma, and cystic astrocytoma. There are 3 potential areas of involvement: cranial nerves, pyramidal tracts, and the cerebellum. Although ataxia can be the presenting complaint, in the absence of hemorrhage or acute CSF obstruction it is unusual for the ataxia to be acute (new during the past 72 hours). Although symptoms may be reported to have developed over the course of days, a careful history typically reveals subtle signs of weakness and coordination difficulties lasting weeks to months. Signs from obstruction of CSF flow are common, and children younger than 2 years typically present with increasing head circumference. In older children, symptoms such as headaches and ataxia are more common. The average time from symptom onset to diagnosis is 7 months. Although less common than brain tumors, spinal tumors can also present with ataxia. Depending on the spinal level, signs of weakness or sensory loss referable to the lower or upper extremities with preservation of reflexes will be present. In addition, as noted previously herein, paraneoplastic presentation of tumors (eg, OMS) at times need to be considered in the differential diagnosis of ataxia.

Miscellaneous Causes

Migraine. Vertigo as the primary or sole manifestation of migraine occurs in 2 settings: with very young children and teenaged girls. Children younger than 4 years can have the abrupt onset of unsteadiness lasting seconds to minutes. More commonly, adolescents describe repeated bouts of isolated vertigo, or headache and vertigo. In both cases, there is usually a family history of migraine and a propensity to motion sickness in the context of a normal neurologic examination.

Psychogenic Conversion Disorder. Another challenge of clinical diagnosis includes a variety of psychogenic conversional mechanisms that impair natural gait. These conversion reactions range from unsteady gait, tripping, falling over, lurching side to side, and advancing to a very disorderly gait of weaving and bobbing called *astasia-abasia*. One meaningful clinical clue to conversional gait patterns is derived from knowledge of physics: periodically standing on one foot while lurching side to side often excludes a primary neurologic cause because neurologically mediated impaired balance leads a patient to widen and lower the stance to lower one's center of gravity. An experienced and patient clinician is required both to work through this difficult differential diagnosis and to communicate with gentle confidence the diagnostic conclusion. For successful management of psychogenic gait disorders, it is essential that parent and physician have a shared confidence in the diagnosis. This facilitates the understanding that is required to comfortably develop and implement the patient- and family-centered intervention based on the use of limited negative laboratory studies and clinical trust.

Metabolic Disease. In the authors' experience, metabolic disease is a very uncommon presentation of acute ataxia. In the era of newborn screening, those disorders, which will present acutely, most commonly do so by age 2 years. A broad range of rare disorders will present later and more insidiously. Nevertheless, particularly in young children, sending an ammonia level is reasonable for unexplained ataxia with vomiting and encephalopathy. Lactate can also be considered. The typical reference range for ammonia is 15 to 45 μg/dL (11–32 μmol/L), but slight elevations are common due to variable collection techniques. However, any value greater than 100 μg/dL (>71 μmol/L) needs to be taken seriously; genetics should be contacted urgently to discuss further management. More generally, metabolic disease should be considered with unexplained relapsing ataxia or encephalopathy, particularly in the setting of fever or illness.

EVALUATION AND THERAPY

A thorough history and physical examination may make laboratory testing unnecessary, for example, with clear-cut migraine or ACA in a well-appearing child. At a minimum, however, urine toxicology should be considered. If there is a high clinical suspicion, blood and urine samples should be held with the intention of sending targeted analysis after consultation with poison control. Lumbar puncture should be considered in the setting of suspected infectious or inflammatory processes, including GBS. Either a normal WBC count or a mild pleocytosis in the CSF is typical in ACA. More significant pleocytosis or a low glucose level in the CSF raises the concern for bacterial meningitis or encephalitis, and an expanded evaluation for viral (especially herpes simplex virus) and bacterial causes is warranted.

Imaging of the brain is indicated in the presence of a focal neurologic finding on examination, or with the inability to perform a reliable neurologic examination in the presence of illness or sedation. Imaging in the absence of these indications is low yield. Acutely, head CT is effective for evaluating for hemorrhage or hydrocephalus. However, MRI of the brain spares the child irradiation and provides more sensitive visualization of the brain parenchyma. Additional studies with contrast are indicated if there is concern for infection and inflammation or tumor. Imaging of the vasculature with magnetic resonance angiography or magnetic resonance venography is useful when stroke is a consideration. Neurologic consultation should typically be obtained before ordering imaging to optimize the study, and before considering conventional cerebral angiography or CT angiography. Spinal cord MRI with and without contrast is useful to evaluate possible cases of ADEM, TM, and GBS. Enhancement of the lumbar roots or cauda equina is an important finding suggestive of GBS or other inflammatory or neoplastic processes in the appropriate clinical setting.

MANAGEMENT

Treatment Approach

Treatment is directed at the underlying diagnosis. Initial attention to vital signs in the ill child is crucial.

Posterior fossa hemorrhage requires urgent neurosurgical consultation. Ischemic stroke requires neurologic consultation and admission to a pediatric critical care unit for further management. In the case of ADEM, immune-modulating therapy, such as corticosteroids, IVIg, or plasma exchange can be considered: treatment can hasten recovery but does not seem to alter the ultimate outcome. A 2004 study of vestibular neuritis in adults found that vestibular function was improved in patients treated with methylprednisolone but not with valacyclovir. Infectious processes, such as cerebellar abscess or brainstem encephalitis, are treated initially with broad antimicrobial therapy (including ampicillin for *Listeria* in the case of brainstem encephalitis) as well as antiviral therapy (acyclovir for herpes simplex virus) until the causative agent is identified. Brain tumors require neurologic, oncologic, and neurosurgical consultation. GBS requires hospital admission for monitoring of vital signs and respiratory function. Treatment with IVIg or plasma exchange speeds recovery, and IVIg is favored because it is less invasive. IVIg should not be used in patients who are immunoglobulin A deficient.

Ongoing Care

Long-term treatment is not typically required for the common causes of pediatric acute ataxia. However, follow-up 2 to 4 weeks after hospital discharge to monitor recovery is reasonable. Prognosis and management are linked to diagnosis. If persistent or permanent dysfunction results, then therapy may require the coordination of physical therapy and sometimes adaptive medical devices. Aside from ingestion, few of the causes of ataxia are preventable. In most cases, the outcome is a good one. For patients requiring hospital admission, early recognition leading to early admission and treatment may improve outcomes.

Summary

- Based on observational studies and expert opinion, (3) for children 28 days to 18 years old with acute ischemic stroke presenting within the treatment window, tissue plasminogen activator should be considered.
- Based on case series and retrospective reviews, (7)(8)(24) acute cerebellar ataxia is typically a benign, self-limited condition. With typical presentation, in the postvaccine era, varicella is an unlikely cause. Lumbar puncture and magnetic resonance imaging of the brain are typically unrevealing and are, therefore, generally not recommended.
- Based on expert opinion, (11) acute disseminated encephalomyelitis should be treated with methylprednisolone, 10 to 30 mg/kg intravenously (IV) daily (maximum of 1 g IV daily), followed by a prednisone taper over 4 to 6 weeks. In severe or refractory cases, based on evidence from case series (12)(13), additional treatment with plasmapheresis or intravenous immunoglobulin (IVIg) should be considered.
- Based on case series and expert opinion, (9)(10) evaluation for occult tumor and treatment with immune therapy is recommended for opsoclonus-myoclonus syndrome.
- Retrospective evidence and expert opinion (19)(20) suggest that treatment of transverse myelitis with early corticosteroids improves outcome. When the diagnosis is being considered, early treatment with methylprednisolone, 30 mg/kg IV (maximum dose, 1 g IV), is recommended, even as other potential causes for acute myelopathy, such as epidural tumor and epidural hematoma, are being evaluated.
- Based on expert opinion, (22) Guillain-Barre syndrome treatment is typically with IVIg, 0.4 g/kg IV daily for 5 days. A multicenter trial of 95 children suggested that treatment hastens recovery and decreases relapse but does not clearly affect overall outcome (23).
- Based on multiple cohort studies (25)(26)(27) of acute flaccid paralysis due to enterovirus D68, empirical therapy with IVIg and/or corticosteroids has been ineffective.
- A randomized study of vestibular neuritis in adults found that vestibular function was improved in patients treated with methylprednisolone but not with valacyclovir (21).

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1. A 7-year-old girl is seen in the emergency department for an unsteady gait. Which of the following findings on her neurologic examination is most likely suggestive of a vestibular dysfunction as the underlying cause of her ataxia?
   - A. Dysdiadochokinesis.
   - B. Horner syndrome.
   - C. Lurching gait.
   - D. Positive Romberg test.
   - E. Pronator drift.
2. An 18-month-old boy is brought to the emergency department for an unsteady gait. He awoke in the morning and had difficulty sitting up on his own and refused to walk. He had been previously healthy apart from an upper respiratory tract infection approximately 1 week earlier. On physical examination he is afebrile, alert, well-appearing, and in no acute distress. His neurologic examination reveals truncal ataxia with difficulty maintaining a seated position and some intention tremor with reaching for objects. When placed on the floor to walk, he will cry and immediately sit down, refusing to walk. There is no nystagmus. Which of the following is the most likely diagnosis in this child?
   - A. Acute cerebellar ataxia.
   - B. Acute intoxication.
   - C. Guillain-Barre syndrome (GBS).
   - D. Opsoclonus-myoclonus syndrome.
   - E. Posterior fossa tumor.
3. The emergency department physician makes the appropriate diagnosis in the patient in question 2 based on the clinical picture. Which of the following is the most appropriate way to counsel the family regarding the prognosis of this condition in this patient?
   - A. At least 90% make a full recovery.
   - B. His condition may progress to obstructive hydrocephalus.
   - C. Less than 50% make a full recovery.
   - D. Less than 50% will worsen, and the remainder will not make a full recovery.
   - E. Prognosis depends on age at diagnosis, with patients younger than 2 years having a better prognosis.
4. The patient from the vignette in questions 2 and 3 returns to the clinic 4 weeks later for follow-up. His symptoms have not resolved. In addition, over the course of a month he has had some developmental regression and has been irritable, sleeping less, and less interactive with the family. On physical examination he is encephalopathic, remains ataxic, and now has emergence of rapid saccadic eye movements. Which of the following diagnoses must be considered at this point in this patient?
   - A. Acute intoxication.
   - B. GBS.
   - C. Labyrinthitis.
   - D. Opsoclonus-myoclonus syndrome.
   - E. Posterior fossa tumor.

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5. An 8-year-old boy is seen in the emergency department for acute onset of ataxia. He also reports a “room-spinning” sensation and emesis. On evaluation he is ill-appearing and holding his head in his hands. Neurologic examination reveals prominent nystagmus, and he reports worsening of his vertigo with movement. He is unable to ambulate without falling over or feeling very nauseated. Which of the following is the most likely diagnosis in this patient?

   A. Acute cerebellar ataxia.
   B. GBS.
   C. Labyrinthitis.
   D. Opsoclonus-myoclonus syndrome.
   E. Posterior fossa tumor.

Acute Ataxia in Children

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Hypoplastic Left Heart Syndrome: An Overview for Primary Care Providers

Rabia Javed, MBBS,* Frank Cetta, MD,*†‡ Sameh M. Said, MD,§ Timothy M. Olson, MD,*†‡ Patrick W. O'Leary, MD,*†‡ Muhammad Yasir Qureshi, MBBS*†

*Wanek Family Program for Hypoplastic Left Heart Syndrome; †Division of Pediatric Cardiology, Department of Pediatric and Adolescent Medicine; ‡Department of Cardiovascular Medicine; §Department of Cardiovascular Surgery, Mayo Clinic, Rochester, MN

Education Gaps

Primary care clinicians should be aware of the physiology of palliation in patients with hypoplastic left heart syndrome. These are patients with complex physiology after staged cardiac operations, and it is often challenging to treat them when they present with other illnesses.

Objectives

After reading this article, readers should be able to:

1. Define hypoplastic left heart syndrome.
2. Discuss the current surgical strategies based on staged palliation.
3. Review the physiology of functional single-ventricle circulation in these patients.
4. Evaluate and treat common illnesses in patients at different stages of palliation.

Abstract

Hypoplastic left heart syndrome is one of the most complex congenital heart diseases and requires several cardiac surgeries for survival. The diagnosis is usually established prenatally or shortly after birth. Each stage of surgery poses a unique hemodynamic situation that requires deeper understanding to manage common pediatric problems such as dehydration and respiratory infections. Careful multidisciplinary involvement in the care of these complex patients is improving their outcome; however, morbidity and mortality are still substantial. In this review, we focus on the hemodynamic aspects of various surgical stages that a primary care provider should know to manage these challenging patients.

AUTHOR DISCLOSURE Drs Javed, Cetta, Said, Olson, O'Leary, and Qureshi have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

HLHS	hypoplastic left heart syndrome
IVC	inferior vena cava
LV	left ventricle
MBTS	modified Blalock-Taussig shunt
PA	pulmonary artery
PDA	patent ductus arteriosus
PGE1	prostaglandin E1
RV	right ventricle
RSV	respiratory syncytial virus
SVC	superior vena cava

INTRODUCTION

Hypoplastic left heart syndrome (HLHS) is a congenital heart defect categorized as a form of functional single ventricle. It consists of a spectrum of anatomical variants characterized by underdevelopment of the left side of the heart. In HLHS, the right ventricle (RV) perfuses both systemic and pulmonary circulations, and the oxygenated blood bypasses the poorly developed left side of the heart through an atrial-level defect and patent ductus arteriosus (PDA). The management strategy for HLHS consists of a series of cardiac operations that culminate in the RV pumping blood to the systemic circulation, while the pulmonary blood flow is provided by passive flow from the superior vena cava (SVC) and inferior vena cava (IVC). Despite the many advances in diagnostic and management strategies in the past 3 decades, patients with HLHS continue to experience major morbidity and mortality. (1)

GENETICS AND EPIDEMIOLOGY

HLHS accounts for 1.4% to 4.1% of all congenital heart diseases, with a prevalence rate of 2 to 3 cases per 10,000 live births in the United States. (2)(3)(4) There is a male predominance, with a reported male to female ratio of 3:2. (5) HLHS is thought to have a complex heterogeneous genetic basis. Specific genes associated with HLHS include *GJA1* (Connexin protein 43), *NKX2-5, NOTCH1, MYH6,* and *ERBB4*. (6)(7) HLHS has been associated with several syndromes, including Jacobsen (terminal deletion of the long arm of chromosome 11), Turner (monosomy X), Edwards (trisomy 18), Patau (trisomy 13), Noonan, Kabuki, Smith-Lemli-Opitz, Holt-Oram, oral-digital-facial, CHARGE (coloboma, heart anomalies, choanal atresia, retardation of growth and development, and genital and ear anomalies) association, and PAGOD (pulmonary hypoplasia, hypoplasia of pulmonary artery, agonadism, omphalocele/diaphragmatic defect, dextrocardia). (8)(9) A genetic association of HLHS with other left-sided obstructive lesions, such as bicuspid aortic valve, coarctation of aorta, Shone complex, and aortic valve stenosis, has been reported. (10)(11)

The recurrence risk of HLHS in families with 1 affected child is approximately 0.5% to 2%. The risk of other congenital malformations in first-degree family members has been reported to range from 10% to 17%. This highlights the importance of performing echocardiographic screening of all first-degree family members of patients with HLHS. (12)(13)(14) This also signifies the requirement of fetal echocardiography if the previous child in the family was diagnosed as having HLHS. In a recent study from Mayo Clinic, familial screening of patients with HLHS found that 11% of 152 first-degree relatives had congenital cardiovascular malformations, of which 65% were undiagnosed before screening echocardiography. (13) Collectively, 27% of patients with HLHS had 1 or more siblings or parents with a congenital heart defect, most commonly bicuspid aortic valve or aortic root dilation.

EMBRYOLOGY AND PATHOGENESIS

In a normal fetus, oxygenated blood from the placenta enters the right atrium via the umbilical vein and ductus venosus. Most of this oxygenated blood (60%) crosses the foramen ovale to reach the left atrium, bypassing the pulmonary circulation. This oxygenated blood is then delivered to the systemic circulation through the aorta, thereby perfusing the brain.

An essential component of normal intrauterine growth of cardiac structures is adequate blood flow through these structures. In HLHS, the mitral and aortic valves are either atretic or hypoplastic, thus decreasing the flow of blood through all left-sided heart structures (mitral valve, left ventricle [LV], aortic valve, and ascending aorta). In utero progression of aortic valve stenosis is one of the integral causes of HLHS. (15) Although bicuspid aortic valve is considered the mildest form of left-sided obstructive lesions, HLHS is at the most extreme end of the spectrum.

Premature closure of the foramen ovale, or other abnormalities of the atrial septum that restrict inflow to the left side of the heart, can be another cause of HLHS. (16) As a result of reduced flow of blood into the left atrium and the LV, the left heart structures do not grow. In late gestation, when HLHS is fully manifest, the flow of blood is from the left atrium to the right atrium across the atrial septum. In the most severe form, the atrial septum is intact. In that case, there is no egress of blood from the left atrium, resulting in pulmonary venous obstruction and hypertension. This impairs development of the pulmonary vasculature in utero and is associated with pulmonary hypertension and poor outcomes after birth.

ANATOMY

HLHS consists of a spectrum of anatomical variants characterized by the underdevelopment of the left side of the heart, which includes the mitral valve, LV cavity, LV outflow tract, aortic valve, ascending aorta, and aortic arch (Fig A). The 3 most common forms are as follows:

1. Aortic valve atresia with mitral valve atresia: This is the most extreme form of HLHS in which the LV cavity is

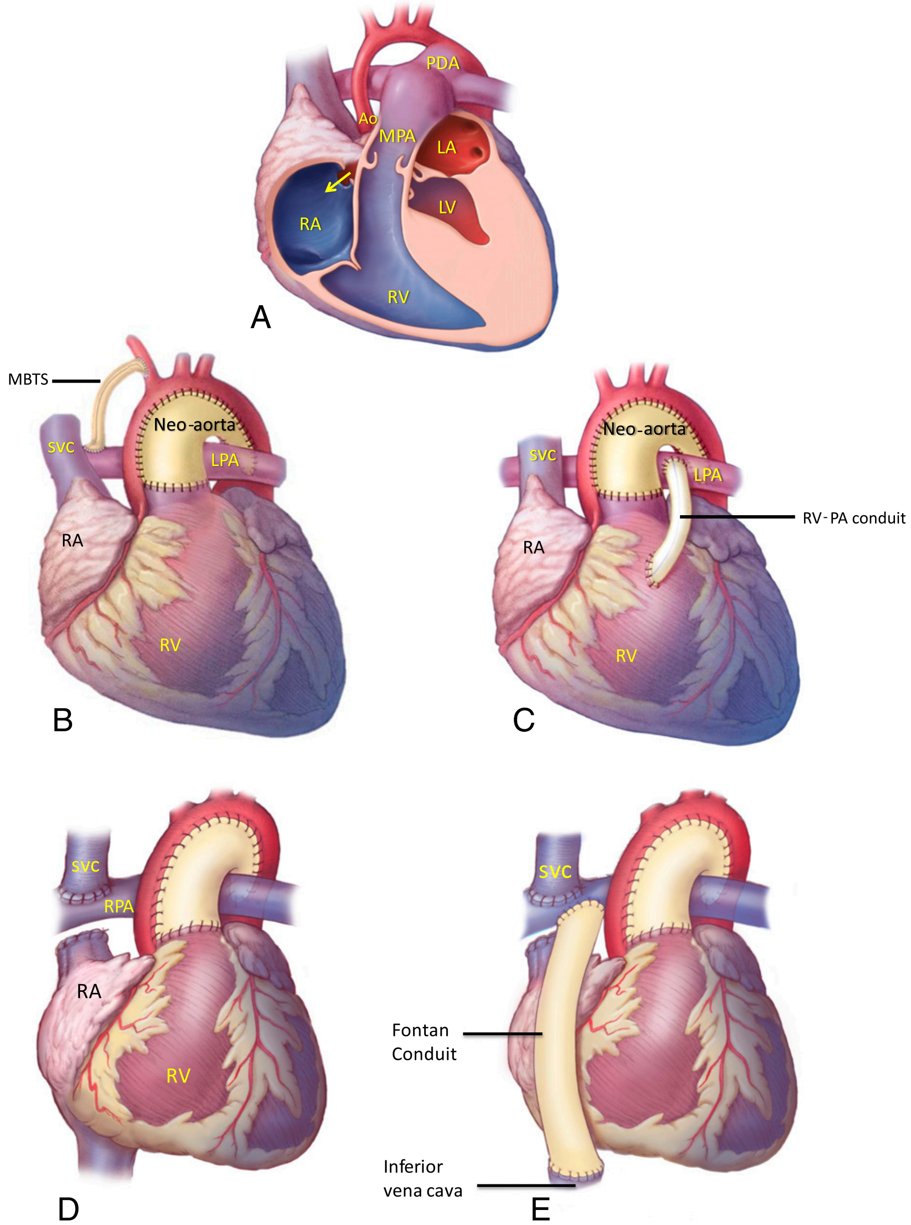

Figure. A. The anatomy of hypoplastic left heart syndrome with underdeveloped left ventricle (LV). The arrow indicates the atrial septum defect. B. Stage 1 palliation using a modified Blalock-Taussig shunt (MBTS). C. Stage 1 palliation using a right ventricle (RV)–to–pulmonary artery (PA) conduit (Sano modification). D. Stage 2 palliation using the bidirectional Glenn shunt. It is a direct anastomosis of the superior vena cava (SVC) to the right PA (RPA). E. Stage 3 palliation. The extracardiac Fontan uses a tube graft to connect the inferior vena cava to the central PA.
Ao=aorta, LA=left atrium, LPA=left pulmonary artery, MPA=main pulmonary artery, PDA=patent ductus arteriosus, RA=right atrium.

very small (almost slitlike) and the ascending aorta and aortic arch are extremely hypoplastic. There is no LV output, so the sole source of blood supply to the systemic circulation is the RV through the PDA.

2. Aortic valve atresia with mitral valve hypoplasia: Due to aortic atresia, the ascending aorta and aortic arch are hypoplastic and the systemic flow again depends on the PDA. The mitral valve is patent and blood enters the LV, but there is no egress. The LV hypertrophies because it contracts against an atretic aortic valve. The thick LV has an ischemic endomyocardium that can result in thick fibrotic tissue known as *endocardial fibroelastosis*. The LV cavity is hypoplastic but its mass can be greater than the first HLHS subtype, resulting in distortion of the RV inflow and tricuspid valve insufficiency.
3. Aortic valve stenosis with mitral valve hypoplasia: As opposed to aortic atresia, stenosis of the aortic valve does permit some egress of blood from the LV, resulting in

less hypoplasia of the LV, ascending aorta, and aortic arch.

Approximately 6% of patients with HLHS have an intact or severely restrictive atrial septum. This morphologic variant is associated with the worst outcome. (17)(18) The restrictive flow of blood across the atrial septum results in high left atrial pressure, resulting in abnormal development of the pulmonary vasculature.

Postnatally, the systemic circulation depends on the presence of adequate interatrial communication and the patency of the ductus arteriosus. The systemic circulation is ductal dependent, and the aortic arch, ascending aorta, and coronary arteries are perfused by reverse or retrograde flow of blood from the PDA. Prostaglandin E1 (PGE1) infusion is essential for these newborns to ensure ductal patency.

DIAGNOSIS AND PRESENTATION

HLHS can be diagnosed prenatally by obstetrical ultrasonography at 18 to 24 weeks. This ultrasonography can identify cardiac malformations that alter the 4-chamber view of the heart. If the left side of the heart appears abnormal, a referral for fetal echocardiography is indicated. A fetal echocardiogram, performed by a pediatric cardiologist, allows detailed ultrasonography that focuses on all the components of the fetal heart. The fetal diagnosis of HLHS depends on the operator's expertise. (19)

The clinical presentation of HLHS depends on the patency of the ductus arteriosus and the degree of restriction of the atrial septum. Neonates with HLHS who were not detected prenatally will present with clinical symptoms or abnormal pulse oximetry screening. This newborn pulse oximetry screen is recommended by the American Academy of Pediatrics and aims to detect critical congenital heart diseases before hospital discharge. A recent study shows that due to the implementation of state newborn screening policies, early infant deaths from critical congenital heart diseases have decreased by 33.4%, with an absolute decline of 3.9 deaths per 100,000 births. (20)

Neonates with a restrictive interatrial communication or intact atrial septum will exhibit cyanosis, respiratory distress, and signs of hemodynamic instability within the first few hours of after birth. Left atrial hypertension leads to pulmonary congestion and early onset of respiratory distress. These neonates require prompt intervention to relieve interatrial obstruction. Intrauterine procedures can also be performed if a prenatal diagnosis of restrictive/intact atrial septum is established. Attempts to create an adequate atrial septal defect in utero have met with varied success. (21)

Some newborns have an adequate interatrial communication, but the patency of the ductus arteriosus is not maintained. These patients usually present within the first week after birth with signs of systemic hypoperfusion manifested as shock, tachycardia, diminished peripheral pulses, and oliguria, which can be addressed with prompt administration of PGE1.

Neonates who have a sufficient interatrial communication and a persistent PDA continue to have adequate systemic perfusion and may initially appear normal. These neonates become symptomatic in the first few weeks after birth, usually after hospital discharge. As the pulmonary vascular resistance declines, they develop signs of pulmonary overcirculation manifested as tachypnea, poor feeding, and cyanosis.

Auscultation typically reveals no murmur. The second heart sound is single and loud due to the absence of an aortic valve component and closure of the pulmonary valve against systemic pressure. A flow murmur across the pulmonary valve can be heard. If there is significant tricuspid regurgitation, it is manifest by a holosystolic murmur.

An electrocardiogram is usually not specific but can show right axis deviation and RV hypertrophy. Similarly, chest radiographs are nonspecific and can show cardiomegaly and pulmonary venous congestion, depending on the degree of left atrial hypertension.

Transthoracic echocardiography is the definitive diagnostic test for HLHS. Depending on the anatomical variant, the echocardiographic views will demonstrate a dilated RV and features of HLHS. To devise a management plan for each patient, echocardiography soon after birth is required to determine the presence of an adequate atrial septal defect and the patency of the ductus arteriosus. In addition, detailed evaluation of the remaining cardiac anatomy and myocardial function is essential for management planning.

MANAGEMENT

The initial management of a patient with HLHS aims to secure ductal patency with a PGE infusion. Depending on the clinical presentation, volume replacement/resuscitation, diuretics, and/or inotropes may be required. Patients with a restrictive or intact atrial septum will need enlargement/creation of an atrial septal defect. (22) This can be performed surgically or via a transcatheter approach.

Current management strategies for infants with HLHS are 3-stage surgical palliation, primary heart transplant, or comfort care. Due to many advances in surgical techniques and medical therapies for patients with HLHS, offering comfort care in the current era to parents of these patients has become less common and remains debatable. (23) Due to the scarcity of organs for transplant, the preferred initial management for HLHS is staged surgical palliation.

The final objective of the 3-stage palliative operations is a Fontan operation. Fontan circulation consists of a single RV as the pump for systemic circulation and passive systemic venous flow for pulmonary perfusion. The goal of the surgical palliation is to achieve an adequate source of pulmonary blood flow, unobstructed coronary artery blood flow, a ductal independent systemic circulation with alleviation of cyanosis, relief of atrial-level obstruction, elimination of pulmonary arterial stenosis, and preservation of RV function.

Stage 1 (Norwood or Hybrid Procedures)

Stage 1 palliative surgery in HLHS is performed in the first week after birth. It aims to provide the RV an unobstructed systemic circulation and establish controlled and balanced flow to the pulmonary circulation.

Oxygenated blood reaches the left atrium from the pulmonary veins. Resection of the atrial septum is performed to establish unhindered flow from the left atrium to the right atrium. The hypoplastic aortic arch is reconstructed with a homograft patch. The main pulmonary trunk is resected, and its proximal part is connected to the ascending aorta. This procedure is sometimes referred to as Damus-Kaye-Stansel. The defect in the distal pulmonary artery (PA) is closed. This allows RV flow to the systemic circulation.

In a classic Norwood procedure, flow to the pulmonary circulation is established by placing a modified Blalock-Taussig shunt (MBTS) from the innominate artery to the PA (Fig B). The MBTS shunt is also known as the modified Blalock-Thomas-Taussig shunt to signify the work contributed by Vivian Thomas. (24) It is constructed with a prosthetic tube. In ideal situations, the MBTS controls flow to the lungs and prevents pulmonary overcirculation and allows adequate delivery of blood to the pulmonary circulation.

One of the disadvantages of the MBTS is that it causes diastolic diversion of blood from the systemic circulation to the pulmonary circulation, negatively affecting the coronary circulation and possibly leading to myocardial ischemia. To overcome this "coronary steal" phenomenon, an alternative to the MBTS was developed. The “Sano modification” creates a tubular connection from the RV to the PA (Fig C). The Sano modification has its own potential disadvantages, with theoretical concerns for arrhythmias or aneurysm formation at the ventriculotomy site.

A multi-institution randomized clinical trial was conducted to assess the results of stage 1 palliation with MBTS versus RV-PA shunts. Investigators in this trial reported that transplant-free survival 12 months after surgery was better with the RV-PA shunt than with the MBTS. However, beyond 12 months of age, no significant difference was observed for either procedure, (25) and there was a higher rate of repeated cardiovascular intervention in patients with the RV-PA shunt.

In high-risk patients with HLHS with preoperative organ dysfunction or infection, where cardiopulmonary bypass should be avoided, a "hybrid" approach is available that uses transcatheter and surgical approaches to achieve the goals of stage 1 palliation. (26) In the hybrid approach, PA bands are placed to limit the pulmonary flow, and a stent is deployed to maintain the ductal patency and ensure flow to the aorta. If required, adequate interatrial communication is established by stent placement or balloon septostomy of the atrial septum. (27) This approach offers benefits to high-risk patients by avoiding the deleterious effects of cardiopulmonary bypass in the newborn period. Issues with this procedure include maintaining ductal stent patency and obstruction of retrograde flow in the aortic arch. Studies are being conducted to assess the outcome of this approach in patients with different risk factors. (28) After stage 1 operation, the systemic oxygen saturation is usually in the 70% to 85% range.

Interstage Monitoring

To improve outcomes after stage 1 palliation, an interstage monitoring program of oxygen saturation and weight is designed for home use. Many patients are discharged from the hospital with a digital scale and pulse oximeter, and parents are advised to obtain daily weights and oxygen saturations. The monitoring program is designed for early recognition of decreased oxygen saturation from baseline and poor weight gain or weight loss. Parents are advised to notify their primary care provider in case of dropping oxygen saturation and failure to gain weight or weight loss. The primary care provider is a vital component of interstage monitoring, and frequent evaluations and communication with a member of the cardiac team are essential for prompt investigations and interventions to rule out complications.

In one study, 157 patients who underwent stage 1 palliation were discharged with home monitoring. Interstage survival was found to be 98%. Fifty-nine percent of the patients in this home monitoring program breached the surveillance criteria. (29) Interstage survival after stage 1 palliation has improved, (30) but there is debate about improvement in long-term survival because many high-risk patients remain in the hospital for prolonged periods between stages 1 and 2. (31)

Stage 2 (Bidirectional Superior Cavopulmonary Connection)

The second stage of palliative surgery for HLHS is performed when patients are 3 to 6 months old. At stage 2, the previous shunt is removed and an anastomosis of the SVC to the right PA is established in what is called a *bidirectional Glenn shunt*. (32) This enables venous blood in the SVC to directly enter the pulmonary circulation (Fig D). Alternatively, a hemi-Fontan procedure can be performed, in which the SVC is not disconnected from the atrium but a patch is placed to exclude SVC flow from entering the right atrium. This patch is eventually removed at the time of Fontan completion. This is a more extensive procedure but it facilitates and augments the subsequent Fontan procedure. (33) Any stenosis of the pulmonary arteries is repaired at this time. After the bidirectional Glenn shunt, systemic oxygen saturation levels are in the low 80%s. By using the hybrid strategy as a first-stage palliation, arch reconstruction is deferred until second-stage surgery. Aortic arch reconstruction at this age can be more complex than a neonatal Norwood aortic reconstruction. (34)

Stage 3 (Fontan Circulation)

The third palliative surgery in HLHS is performed between 18 months and 4 years of age. Choussat et al (1977) outlined selection criteria to define an ideal candidate for a Fontan procedure. (35) An ideal candidate for a Fontan procedure is older than 4 years, has mean PA pressure less than 15 mm Hg, and has pulmonary arteriolar resistance less than 4 Wood units/m^2. Patients with a good long-term outcome after Fontan operation generally have normal systolic and diastolic ventricular function and not more than mild tricuspid regurgitation, and they maintain sinus rhythm. Unfortunately, many patients with HLHS struggle with these features of a "good Fontan." However, recently, younger patients with HLHS are being moved toward the Fontan than what was initially described by Choussat et al.

The goal of Fontan circulation is to route blood from the IVC to the pulmonary arteries. In this way, all systemic venous blood flows directly into the pulmonary circulation, without being pumped, bypassing the heart. This flow is passive and depends on higher central venous pressure and lower pulmonary vascular resistance. Negative intrathoracic pressure during normal breathing facilitates this passive pulmonary perfusion. Moreover, the complex physiology of Fontan circulation also depends on the ventricular end diastolic pressure. Typically, the IVC is disconnected from the atrium, and a large-bore Gore-Tex (W. L. Gore & Associates GmbH, Feldkirchen-Westerham, Germany) tube graft is used to connect it to the central PA. This procedure is known as an "extracardiac" Fontan (Fig E). In the alternative method, a lateral tunnel Fontan, a wall is created inside the right atrium connecting the IVC to the SVC and pulmonary arteries in the heart. Unfortunately, Fontan physiology has negative long-term effects on other organ systems that sometimes are not manifest for several decades. (36)

COMMON PEDIATRIC PROBLEMS AT VARIOUS STAGES OF PALLIATION

Feeding Problems

Patients with HLHS have a high metabolic and nutritional demand in the setting of major cardiac operations and wound healing. In addition, there are several periods of no enteral feedings due to sedation or high-dose vasopressors. These patients also experience a high incidence of necrotizing enterocolitis. Adequate caloric intake must be assessed and addressed every day in the hospital and on every outpatient clinic visit. Maximizing caloric intake is necessary to achieve normal growth. Because surgical intervention begins in the neonatal period and these patients experience prolonged ICU stays, feeding problems are very common in children with HLHS. The sedation needed for invasive procedures and the lack of oral stimulation frequently results in oral aversion. Early involvement of occupational therapy and bedside nursing focused on feeding issues can reduce this problem. Many patients may require tube feeding to ensure adequate caloric intake. Need for gastrostomy tube placement in this patient group is not uncommon. The Feeding Work Group of the National Pediatric Cardiology Quality Improvement Collaborative has conducted a literature review to assess the best nutrition practices in various participating centers to outline nutrition algorithms for infants with HLHS. (37)

Dehydration

Children with HLHS can acquire gastrointestinal viral infections similar to any other child. However, they do not tolerate dehydration very well. In addition, many of these children are taking diuretics, and this makes them even more vulnerable to dehydration. After stage 1 surgery, dehydration may precipitate shunt occlusion. Although all children are treated prophylactically with aspirin, the MBTS or Sano shunt may thrombose in the setting of intravascular volume depletion due to sluggish blood flow. This may lead to decreased blood flow to the lungs, resulting in a profound hypoxia. A shunt murmur may not be audible in this situation, and an echocardiogram should be performed emergently to assess shunt flow. An emergency surgical or transcatheter intervention may be needed to reestablish pulmonary perfusion. If the shunt is patent, euvolemia should be achieved by oral or intravenous fluid resuscitation.

After stage 2 and 3 surgery, dehydration should be avoided, but the presentation is not as dramatic or life-threatening. Hypovolemia after stage 2 and 3 leads to decreased central venous pressure. A relatively high central venous pressure is needed to have passive flow of blood from the venae cavae to the pulmonary circulation. Fluid resuscitation should be performed boldly, without fear of developing pulmonary edema in this setting.

Respiratory Infections

Viral respiratory infections are common in children and can become life-threatening in those with HLHS. After stage 1 palliation, the balance between the pulmonary and systemic circulation is maintained by the size of the MBTS or Sano shunt and the pulmonary vascular resistance relative to the systemic vascular resistance. Pulmonary vascular resistance is increased with respiratory infections, disrupting this balance and resulting in hypoxia. Pulmonary vasodilation is used to reestablish this balance and alleviate hypoxia. Supplemental oxygen is the easiest and quickest way to achieve pulmonary vasodilation. Proper pulmonary toilet is essential. Mechanical ventilation with inhaled nitric oxide may be needed in severe respiratory compromise.

After stage 2 and 3 surgeries, the increase in pulmonary vascular resistance from respiratory infection has a slightly different hemodynamic effect and is managed slightly differently. However, it still presents with hypoxia. Here the passive pulmonary blood flow depends on low pulmonary vascular resistance. Therefore, the increase in pulmonary vascular resistance impairs pulmonary perfusion, resulting in hypoxia. Pulmonary vasodilation by administering supplemental oxygen, and sometimes inhaled nitric oxide, is used to decrease the pulmonary vascular resistance. Contrary to stage 1 surgical patients, intubation and positive pressure mechanical ventilation should be avoided if possible after Glenn and Fontan operations because negative intrathoracic pressure from normal breathing assists passive pulmonary perfusion after stages 2 and 3. In addition, intravenous fluid administration can also help with pulmonary perfusion by increasing the central venous pressure.

Immunizations

Patients with HLHS are a high-risk population, and immunization is an essential part of their health-care. Respiratory tract infections, particularly respiratory syncytial virus (RSV) and influenza, are a cause of morbidity and mortality during the interstage period in patients with HLHS. These patients require hospitalization, cardiopulmonary bypass, and blood component transfusion, and so it is very important for the primary care provider and cardiac team to coordinate time frames for their optimal immunization. Preventive measures and education of the families regarding hand hygiene and immunizations can play a major role in improving mortality and morbidity in this group. Inactivated influenza vaccine is recommended in all children older than 6 months. (38)(39) Regarding prophylaxis against RSV, administration of palivizumab in infants with HLHS should be made in consultation with a pediatric cardiologist. An individualized approach should be taken for each patient regarding their hemodynamic status and timings of the surgery. (40)(41) Routine immunization has not been reported to be associated with any adverse outcomes in these patients. (42) The National Pediatric Cardiology Quality Improvement Collaborative has led an initiative toward quality improvement in the interstage period, with one of the goals being to discuss and document immunization status and plan for RSV and influenza prevention at every clinic visit. (43)

Neurodevelopmental Outcomes

Patients with HLHS are at high risk for neurodevelopmental delays and impaired brain growth and maturation. (44) The neurodevelopmental disabilities include changes in visual motor integration, motor and language deficits, and cognitive dysfunction. In evaluation of the school-aged children who had undergone staged palliation, an increase in the prevalence of attention-deficit/hyperactivity disorder was found. (45) Early recognition of the delays and longitudinal surveillance throughout childhood and into adulthood are necessary to prevent adverse outcomes in these patients. The guidelines for the neurodevelopmental care of children with congenital heart diseases are outlined by the American Heart Association. The guidelines recommend frequent systemic evaluations of the patients' developmental monitoring and recognition of the need for early interventions. (46)

Antimicrobial Prophylaxis for the Prevention of Bacterial Endocarditis

According to the American Heart Association guidelines, last revised in 2007, patients with cyanotic or palliated cardiac conditions are at high risk for adverse outcome from infective endocarditis. (47) Therefore, before any dental procedure, antimicrobial prophylaxis for the prevention of bacterial endocarditis is suggested in patients with HLHS. This remains true even after Fontan operation.

PROGNOSIS

Survival of patients with HLHS has improved during the past 3 decades. (48) Before development of the Norwood procedure, the only option was to provide comfort care to these patients. Hospital survival after stage 1 palliation has improved from 53% (1992–1996) to 93% (1996–2001). (49) However, the interstage (between stage 1 and 2 surgeries) mortality rate continues to be high. Those who make it to the Fontan procedure have better survival rates but are burdened by other long-term complications. (50) The long-term complications after Fontan procedure continue to be a major concern and are beyond the scope of this article. (36) Further efforts are required to decrease the morbidity and mortality associated with HLHS.

Summary

- Based on strong research evidence, hypoplastic left heart syndrome (HLHS) is a critical congenital heart disease associated with high morbidity and mortality. (1)(4)
- Based on strong research evidence, the current management approach for infants with HLHS is 3-stage surgical palliation. The final objective of the 3 cardiac operations is to achieve Fontan circulation, consisting of a single right ventricle as the pump for systemic circulation, and passive pulmonary perfusion from the systemic venous return. Patients with HLHS have complex and unique physiology after each surgical stage. (32)(48)(49)(51)
- Based on expert opinion, due to lack of relevant clinical studies, in patients who experience life-threatening respiratory infections, intubation and positive pressure mechanical ventilation should be avoided after Glenn and Fontan operations.
- Based on expert opinion, due to lack of clinical studies, a cautious approach is required to evaluate and treat dehydration in patients with HLHS. After stage 1 surgery, dehydration may precipitate shunt occlusion; therefore, fluid resuscitation should be accompanied by complete evaluation of the shunt.

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References for this article are at http://pedsinreview.aappublications.org/content/40/7/344.

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1. You are following in your clinic a 3-year-old boy with a history of hypoplastic left heart syndrome (HLHS). The patient is doing well and is being followed by cardiology. He underwent 2 stages of the 3-stage palliative surgical procedures. The mother informs you that she is 18 weeks pregnant and that the cardiologist has recommended a fetal echocardiographic screening to look for any type of associated congenital heart defect, not just HLHS. Of the following congenital heart defects, which is the most common defect that affects siblings or parents of patients with HLHS?
   - A. Bicuspid aortic valve.
   - B. Coarctation of the aorta.
   - C. HLHS.
   - D. Patent ductus arteriosus.
   - E. Tetralogy of Fallot.
2. A primigravida pregnant woman at 39 weeks' gestation is admitted to the labor and delivery suite in active labor. She had prenatal care and the baby was diagnosed as having HLHS on prenatal ultrasonography. In addition to the obstetrics team, the neonatologist, cardiologist, and NICU transport team are present during delivery. After 4 hours of labor she delivers a male newborn. In addition to the routine postdelivery interventions, which of the following measures is the most critical for the continued survival of this patient?
   - A. β-blocker infusion.
   - B. Echocardiography.
   - C. Indomethacin infusion.
   - D. Prostaglandin E1 (PGE1) infusion.
   - E. Twelve-lead electrocardiography.
3. The patient in question 2 was admitted to the NICU, placed on a monitor, and given PGE1. On physical examination the baby looks well-perfused, with no labored breathing. Heart examination reveals a loud single S2 and a grade III holosystolic murmur best heard over the tricuspid area. Which of the following is the best diagnostic test to confirm the diagnosis of HLHS in this patient?
   - A. Cardiac computed tomography.
   - B. Cardiac enzyme levels.
   - C. Electrocardiography.
   - D. Magnetic resonance angiography.
   - E. Transthoracic echocardiography.
4. The diagnosis of HLHS is confirmed in this patient. A family care conference was held to discuss the management plan options with the family. Which of the following is the most appropriate initial management plan in this patient?
   - A. Discharge the patient and intervene if signs of decompensation occur.
   - B. Heart transplant after 2 years of age.
   - C. Immediate heart transplant.
   - D. Supportive and comfort care until a suitable heart donor is found.
   - E. Three-stage surgical palliation, with the first stage to start at 1 week of age.

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5. A 6-year-old boy is brought to the clinic for a health supervision visit. His medical history is significant for HLHS status post 3-stage surgical palliative procedures, the last of which was the Fontan procedure performed at 4 years of age. Which of the following health maintenance interventions is recommended in this patient?
   - A. Avoid live virus vaccines.
   - B. Bacterial endocarditis prophylaxis before dental procedures.
   - C. Immunizations are contraindicated.
   - D. Restrict caloric intake due to lower activity level.
   - E. Restrict fluid intake to prevent fluid overload.

Hypoplastic Left Heart Syndrome: An Overview for Primary Care Providers

Rabia Javed, Frank Cetta, Sameh M. Said, Timothy M. Olson, Patrick W. O'Leary and Muhammad Yasir Qureshi

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Pediatric Hypertension: Review of Updated Guidelines

Donald J. Weaver, Jr, MD, PhD*

**Division of Nephrology and Hypertension, Department of Pediatrics, Levine Children's Hospital at Carolinas Medical Center, Charlotte, NC*

INTRODUCTION

After the publication of my review on pediatric hypertension, the American Academy of Pediatric's Subcommittee on Screening and Management of High Blood Pressure in Children issued new Clinical Practice Guidelines for Screening and Management of High Blood Pressure in Children and Adolescents. (1)(2) These guidelines represent an update to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents that was published in 2004. (3) For the new guidelines, the subcommittee consisted of 17 members and was co-chaired by a pediatric nephrologist and a general pediatrician. To develop these recommendations, an extensive literature review addressing the diagnosis, management, and treatment of pediatric hypertension was conducted. Articles were then reviewed by 2 subcommittee members. Selected articles were then evaluated for quality of evidence based on an AAP grading matrix. From this, 30 key action statements were developed. In addition, 27 additional recommendations based on consensus expert opinion were also provided. Herein I highlight 7 significant changes in the initial screening and management of pediatric patients with hypertension that are important to primary care pediatricians.

New Definitions of Pediatric Hypertension

Recently, the American Heart Association and the American College of Cardiology updated the definition of adult hypertension based on large observational studies that established a graded association between increased blood pressure (BP) and risk of cardiovascular disease, end-stage renal disease, and mortality. (4) Specifically, a meta-analysis of 61 prospective studies determined that the risk of cardiovascular disease increased beginning at systolic BP levels less than 115 mm Hg and diastolic BP levels less than 75 mm Hg. The risk of death from ischemic heart disease and stroke increases linearly with BPs higher than 115/75 mm Hg. Therefore, the cutoff values for adult hypertension have been lowered. Stage 1 hypertension is now defined as a BP of 130/80 to 139/89 mm Hg, and stage 2 hypertension is now defined as a BP greater than or equal to 140/90 mm Hg.

To be more consistent with these recommendations, the new pediatric guidelines also updated the definitions of pediatric hypertension (Table 1). For children 1 to less than 13 years of age, elevated BP is defined as a BP equal to or greater than the 90th percentile to less than the 95th percentile or between 120/80 mm Hg and less than the 95th percentile. Stage 1 hypertension is a BP equal to or greater than the 95th percentile and less than the 95th percentile + 12 mm Hg or 130/80 to 139/89 mm Hg. Stage 2 hypertension is a BP equal to

AUTHOR DISCLOSURE Dr Weaver has disclosed that he is a member of the speakers' bureau for Alexion Pharmaceuticals. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
BMI	body mass index
BP	blood pressure
DASH	Dietary Approach to Stop Hypertension

TABLE 1. **Updated Definitions of Pediatric BP Categories and Stages**

	FOR CHILDREN AGED 1–<13 Y	FOR CHILDREN AGED ≥13 Y
Normal BP	<90th percentile	<120/<80 mm Hg
Elevated BP	≥90th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower)	120/<80–129/<80 mm Hg
Stage 1 HTN	≥95th percentile to <95th percentile + 12 mm Hg or 130/80–139/89 mm Hg (whichever is lower)	130/80–139/89 mm Hg
Stage 2 HTN	≥95th percentile + 12 mm Hg or ≥140/90 mm Hg (whichever is lower)	≥140/90 mm Hg

BP=blood pressure, HTN=hypertension.

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or greater than the 95th percentile + 12 mm Hg or greater than or equal to 140/90 mm Hg. For children 13 years and older, an elevated BP is defined as a systolic BP of 120 to 129 mm Hg and a diastolic BP less than 80 mm Hg. Stage 1 hypertension is a BP between 130/80 and 139/89 mm Hg. Finally, stage 2 hypertension is a BP equal to or greater than 140/90 mm Hg. It is also important to note that the term *prehypertension* has been replaced by *elevated BP*.

New Normative BP Tables

Current definitions of pediatric BPs are based on normative data in healthy children because of the lack of long-term outcome data. In the current guidelines, new BP tables were developed that include systolic BP as well as diastolic BP based on age, sex, and height. Similar to the Fourth Report, the values are based on auscultatory measurements of approximately 50,000 healthy children and adolescents. The primary difference is that the current tables include only BP values from patients with a body mass index (BMI) less than the 85th percentile or normal weight for height. The subcommittee made the decision to exclude overweight and obese patients based on the strong association between elevated BPs and elevated BMI. The primary implication of these changes for practicing physicians is that the BP cutoffs in the new tables are lower than those in the Fourth Report, and electronic medical records that flag elevated values based on the previous guidelines will need to be updated. The authors did provide a simplified table to facilitate recognition of BP values that require additional follow-up in the current guidelines (Table 2).

Change in the Frequency of BP Measurement

The Fourth Report recommended that all patients 3 years or older in the medical setting should have a BP measurement, including both well and sick visits. In the new guidelines, healthy children 3 years and older should have their BP measured annually. However, children at risk for hypertension, including patients with obesity, chronic kidney disease, or diabetes or taking medications that increase BP, should continue to have BPs monitored at every health-care encounter. Similarly, patients who are younger than 3 years with conditions known to increase BPs, such as prematurity, chronic kidney disease, and malignancy, should also have their BPs measured annually.

Initial Management of Office-Based Elevated BPs

The current guidelines provide more specific recommendations for the initial management and follow-up of office-based elevations in BP (Fig 1). First, wrist and forearm BP measurements are not recommended in children and adolescents. Similar to previous guidelines, initial BPs may be obtained using an oscillometric device with an appropriately sized cuff on the right arm. If the BP is greater than the 90th percentile, repeated BP measurements performed by auscultation should be obtained and averaged. If the averaged BP is normal or less than the 90th percentile, BPs should be monitored as discussed previously herein. However, if elevated, 2 additional auscultatory readings should be obtained and averaged. If these BPs are greater than the 90th percentile, the current recommendations are as follows. For elevated BPs, lifestyle recommendations should be implemented and a repeated BP measurement scheduled in 6 months. If the 6-month BP is elevated, upper and lower extremity BPs should be obtained, lifestyle changes should be reiterated, and BP should be rechecked in 6 months. If after a year BPs remain elevated, ambulatory BP monitoring (ABPM) should be obtained and a diagnostic evaluation should be completed. For the asymptomatic child with BP

TABLE 2. **Screening BP Values Requiring Further Evaluation**

	BLOOD PRESSURE, MM HG			
	BOYS		GIRLS	
AGE, Y	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

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consistent with stage 1 hypertension, lifestyle changes should be addressed and the BP rechecked in 1 to 2 weeks. If the reading continues to be abnormal, upper and lower extremity measurements should be obtained with consideration of nutrition referral or weight management as a well as a repeated measurement in 3 months. If the elevations persist after 3 visits, ABPM should be obtained and a diagnostic evaluation should be initiated. Subspecialty referral is also suggested at this stage. For stage 2 hypertension, upper and lower extremity readings should be obtained, with a repeated measurement within a week. If the reading remains consistent with stage 2 hypertension on repeated

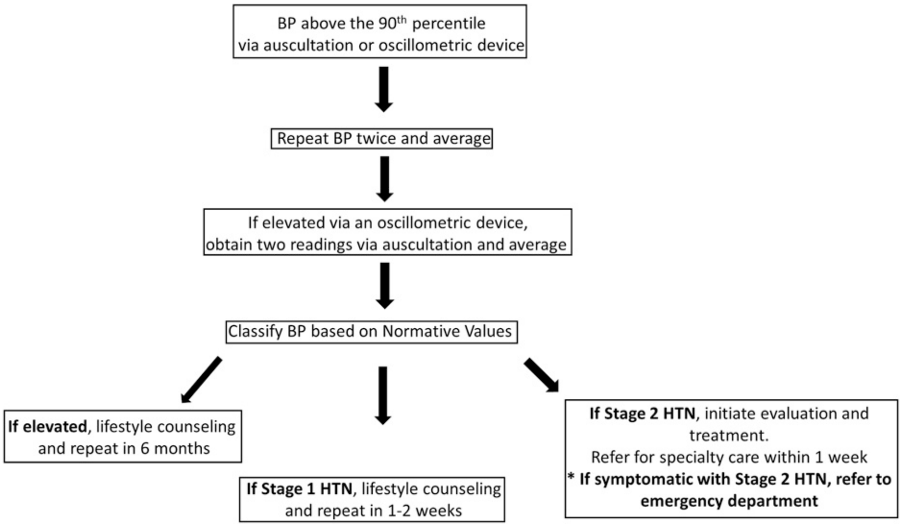
BP above the 90th percentile via auscultation or oscillometric device
Repeat BP twice and average
If elevated via an oscillometric device, obtain two readings via auscultation and average
Classify BP based on Normative Values
If elevated, lifestyle counseling and repeat in 6 months
If Stage 1 HTN, lifestyle counseling and repeat in 1-2 weeks
If Stage 2 HTN, initiate evaluation and treatment.
Refer for specialty care within 1 week
* **If symptomatic with Stage 2 HTN, refer to emergency department**

Figure 1. Algorithm for the evaluation of initial elevation in office-based blood pressures (BPs). HTN=hypertension.

measurement, a diagnostic evaluation including ABPM as well as treatment of those elevated BPs should be initiated. Any patient with symptomatic stage 2 hypertension or BP more than 30 mm Hg higher than the 95th percentile should be treated urgently in the emergency department or inpatient setting.

Expanded Use of ABPM

As discussed in the previous review, ABPM involves a BP cuff and associated recording device that measures BP every 15 to 30 minutes during the day and night outside of the medical setting. These readings are then analyzed using separate guidelines. (5) Recent pediatric data suggest that ABPM is more accurate than office-based BP measurements. More importantly, end-organ changes, such as left ventricular hypertrophy, are more closely associated with ABPM-based readings than office-based BP readings. As a result, the new guidelines recommend that ABPM should be used in children and adolescents to confirm elevated office-based BP readings. Certainly, in children 5 years or younger, this may be technically difficult. Also, ABPM should be considered annually in children with high-risk conditions, such as chronic kidney disease or diabetes. This recommendation is based on the finding that masked hypertension (normal office-based BPs but abnormal ABPM) is associated with increased risk of end-organ damage and is prevalent in patients with chronic kidney disease.

A More Limited Diagnostic Evaluation

Recent studies suggest that primary hypertension is the most common diagnosis of hypertension in children. As a result, the new guidelines recommend a limited diagnostic evaluation for children and adolescents 6 years or older with findings of secondary hypertension on history or physical examination, particularly children with a positive family history of hypertension and a BMI greater than the 85th percentile. Screening tests should include a urinalysis, chemistry panel (electrolytes, blood urea nitrogen, and creatinine), and lipid panel. In patients with a BMI greater than the 95th percentile, hemoglobin A1c, aspartate aminotransaminase, alanine aminotransaminase, and a fasting lipid panel should be obtained. Renal ultrasonography is recommended in all patients younger than 6 years or in those 6 years or older with an abnormal urinalysis finding or abnormal renal function. Additional studies should be obtained based on history, physical examination, and abnormalities on screening laboratory studies.

An additional key action statement in the new guidelines recommends against the use of electrocardiography in children with hypertension because of poor sensitivity. Instead, echocardiography should be performed to assess for changes in left ventricular mass, geometry, or function when pharmacologic therapy is considered for the treatment of hypertensive children. Repeated echocardiography should be performed at 6- to 12-month intervals in patients with refractory hypertension despite treatment, the presence of left ventricular hypertrophy, or impaired cardiac function. Annual evaluation should also be considered in patients with stage 2 hypertension or secondary hypertension. Routine assessment of uric acid, microalbuminuria, pulse wave velocity, or carotid intimal thickness as surrogates for increased cardiovascular risk is not recommended in the new guidelines.

New Treatment Goals

Consistent with the previous guideline, lifestyle interventions are the initial recommendation for treatment of hypertension in children and adolescents. Specifically, the Dietary Approach to Stop Hypertension (DASH) diet and moderate to vigorous physical activity 3 to 5 days a week should be initiated. The DASH diet recommends increasing the servings of fresh vegetables and fruits, limiting foods high in sugars, and choosing lean protein sources as well as fat-free or low-fat dairy products. Pharmacologic treatment should be considered for patients who fail lifestyle interventions, who have symptomatic hypertension, who have stage 2 hypertension, or who have hypertension in the setting of chronic kidney disease or diabetes. The current guidelines recommend that regardless of lifestyle modifications or pharmacologic treatment, goal BPs should be a decrease in systolic and diastolic values to less than the 90th percentile or less than 130/80 mm Hg in patients 13 years or older. Moreover, patients with chronic kidney disease should be treated to lower BP to less than the 50th percentile based on 24-hour ABPM.

In children with hypertension and chronic kidney disease, proteinuria, or diabetes mellitus, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker is recommended as the initial medication unless there are other contraindications. Otherwise, an angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, long-acting calcium channel blockers, and thiazide diuretics are appropriate initial agents. α-Blockers, β-blockers, centrally acting agents, vasodilators, and potassium-sparing diuretics should be used in patients whose hypertension is refractory to 2 or more agents.

CONCLUSION

As noted previously herein, the prevalence of hypertension in the pediatric population is increasing, in part related to worsening obesity. More concerning, hypertension in children is often underdiagnosed. Based on knowledge gained in the past 14 years since publication of the Fourth Report, the current Clinical Practice Guideline aims to improve the recognition, evaluation, and treatment children and adolescents with hypertension. The new guideline also highlights the need for ongoing research in pediatric hypertension to improve patient outcomes.

References for this article are at http://pedsinreview.aappublications.org/content/40/7/354.

Pediatric Hypertension: Review of Updated Guidelines

Donald J. Weaver Jr

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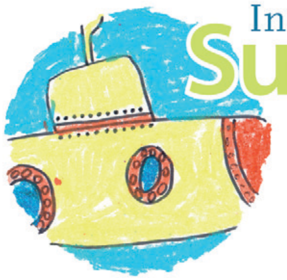

Index of Suspicion

1

Delayed Diagnosis in a 13-year-old with Persistent Neurologic Symptoms after a Carnival Ride

Elizabeth J. Thompson, MD,* Benjamin Wildman-Tobriner, MD,†
Victoria Parente, MD, MPH*

Department of Pediatrics, †Department of Radiology, Duke University Health System, Durham, NC

EDITOR'S NOTE

For some of us, summer offers time to get rejuvenated and refreshed so we can return with positive energy as we get back into the "flow" of patient care activities. The notion of flow was popularized a decade ago by Mihaly Csikszentmihalyi in the bestseller *Flow: The Psychology of Optimal Experience*. Satisfaction with daily experiences was said to best result when we mindfully engage in a flowing state of consciousness that provides creativity and enjoyment.

Similarly, physical health is impaired when organ systems are hindered from allowing body fluids to flow normally. This month's *Index of Suspicion* cases include examples of altered blood and intestinal flow. Enjoy working through interesting diagnostic thought processes.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A previously healthy 13-year-old girl presented to her local emergency department with headache, word-finding difficulty, and transient vision changes after a carnival ride. Results of a noncontrast head computed tomographic (CT) scan were normal, and she was discharged from the local emergency department.

Over the next 2 weeks her headache and intermittent word-finding difficulty persisted. She also developed paresthesia of the right hemibody and had trouble completing schoolwork. These symptoms prompted self-referral to a neurologist, who performed an electroencephalogram that was significant for left-sided slowing. The neurologist referred her to the hospital for further evaluation.

On arrival at our hospital her vital signs are normal and she is not experiencing neurologic symptoms. Her physical examination reveals a 2/6 systolic ejection murmur. She is neurologically intact, with no visual, motor, or sensory deficits. Coagulation studies, inflammatory markers, complete blood cell count, and electrolytes are within normal limits. The antinuclear antibody titer is moderately positive at 1:640. Findings from echocardiography with a bubble study are normal. Imaging studies lead to the diagnosis.

AUTHOR DISCLOSURE Drs Thompson, Wildman-Tobriner, and Parente have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

DISCUSSION

Before obtaining further imaging, the differential diagnosis was broad and included complex migraine, concussion, seizure, anxiety, transient ischemic attack, carotid artery dissection (CAD), electrolyte abnormalities, coagulopathies, and autoimmune disorders such as systemic lupus erythematosus and multiple sclerosis. Many of these disease processes can present with focal neurologic symptoms; however, given the proximity of her symptoms to the carnival ride, trauma was thought to be a main contributing factor and helped narrow the differential diagnosis.

CT angiography revealed smooth tapering of the extracranial left internal carotid artery (ICA) and absence of flow in the supraclinoid ICA (Fig 1A). These findings were concerning for CAD, which was confirmed by conventional cervicocerebral angiography (Fig 1B). Neurosurgery was consulted and recommended medical management with aspirin. Ultimately, it was thought that neck hyperextension from the carnival ride caused the dissection. Her neurologic symptoms were attributed to ischemic changes from ICA occlusion.

The Condition

CAD can lead to arterial narrowing, occlusion, and even ischemic stroke. (1) With an annual incidence of 3 per 100,000 in pediatric patients, CAD represents a major cause of stroke in children. (2) Most patients with CAD are boys aged 8 to 10 years, and the most common mechanisms of injury include direct blunt trauma to the head or neck, intraoral injury, or forceful hyperextension of the neck. (2)(3) Less commonly, CAD is associated with more inconsequential mechanisms of injury, such as after exercise or sporting events, fitness video game practice, sneezing, sexual intercourse, waterskiing, or, as in this case, a carnival ride. (4)(5)(6)(7) A similar finding of an ICA dissection leading to ischemic stroke has been reported in a 4-year-old patient after a roller coaster ride. (8) Spontaneous dissection can be associated with underlying disease processes such as Marfan syndrome, Ehlers-Danlos syndrome, fibromuscular dysplasia, and osteogenesis imperfecta. (9) If no clear mechanism for dissection is identified, further evaluation may be warranted.

Because CAD is a rare phenomenon in children, general practitioners may not consider it when a patient presents with neurologic symptoms; however, early recognition and intervention has the potential to prevent serious morbidity, such as stroke or even death. (10) The most common presenting symptoms of CAD are headache and focal neurologic deficits consistent with stroke, such as aphasia, hemiparesis, ataxia, facial palsy, and somnolence. However, in some cases, physical examination findings may be normal. (11) Therefore, if a patient presents asymptomatically after a high-risk mechanism of injury, further evaluation may be warranted. In addition, CAD should be considered even without an obvious high-risk mechanism of injury if there is an abrupt onset of focal neurologic symptoms after seemingly mundane head and neck movements.

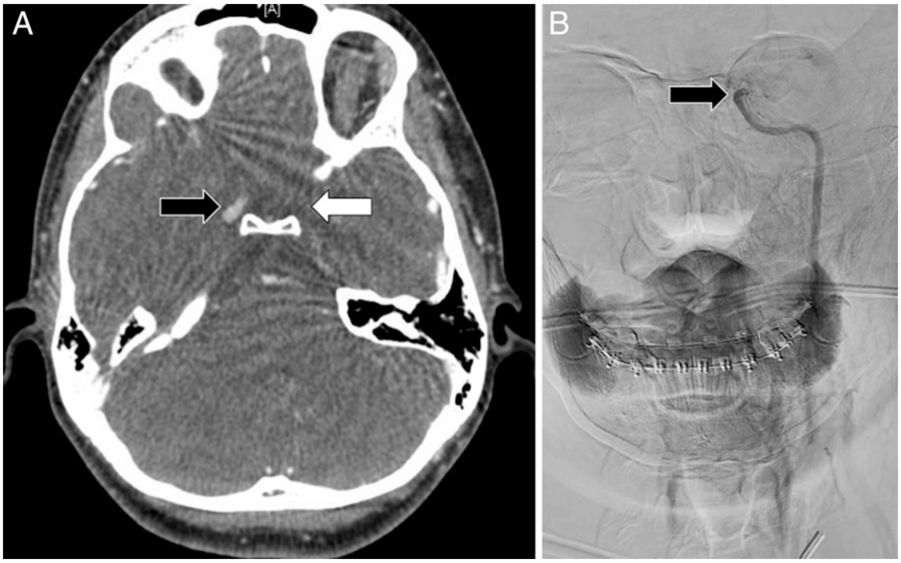

Figure 1. Imaging at the time of presentation. A. Computed tomographic angiogram showing nonopacification of the supraclinoid internal carotid artery (ICA) on the left (white arrow). Normal flow is seen on the right at the same level (black arrow). B. Digital subtraction angiogram. Injection of the left carotid artery shows delayed and diminutive flow throughout a narrowed left ICA, with abrupt tapering at the level of the ophthalmic artery (black arrow). No flow is seen in the middle cerebral artery or its branches.

If there is a high suspicion of CAD based on mechanism of injury and/or physical examination findings, the provider should immediately refer the patient for imaging at a hospital with neurosurgery available and consider starting antiplatelet therapy to prevent the occurrence or recurrence of stroke. (12)

Diagnosis and Management

Angiography is essential for diagnosis and is available in multiple forms. Conventional angiography remains the gold standard and also offers the option for treatment (stent placement). However, it is not without risk; some patients may develop neurologic deficits after angiography. (12) CT angiography allows for rapid imaging with accuracy close to conventional angiography and is typically widely available. Magnetic resonance angiography is another option but is not always appropriate in the acute setting and is less accurate than conventional angiography. Carotid ultrasonography with Doppler technique is another option, but visualization is often limited, and the study is operator dependent. (13)

Treatment for CAD consists of either antiplatelet or anticoagulation therapy to prevent the occurrence or recurrence of stroke. (14) Recurrence rates of stroke are similar between the two, and, thus, antiplatelet therapy is most commonly used because it requires less monitoring and has a safer pharmacologic profile. (12) Surgical and endovascular interventions, such as carotid angioplasty and stenting, are reserved for progressive or recurrent symptoms. (12)(14)

Patient Course

Our patient remained clinically stable throughout her hospital stay and returned to neurologic baseline without surgical intervention. She was started on aspirin (325 mg) daily and then transitioned to 81 mg of aspirin daily after 3 months. She will continue this for life. Imaging obtained 3 and 6 months after injury showed stable left ICA occlusion. Despite some reconstitution of blood flow from the posterior communicating artery, there was persistently diminished perfusion to the left middle and anterior cerebral arteries (Fig 2). She was able to resume sports 6 months after injury, and her school performance returned to baseline.

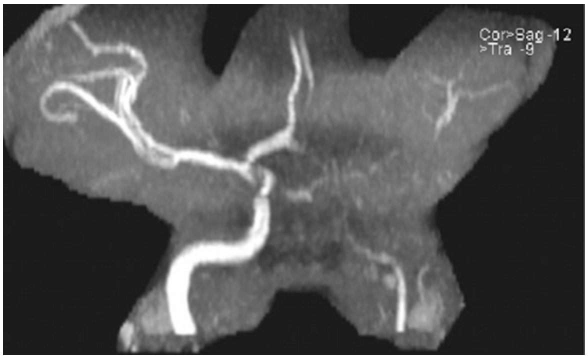

Figure 2. Magnetic resonance angiogram 6 months after the initial injury. Anterior maximum-intensity projection image shows persistent poor flow through the left internal carotid artery, with minimal flow in the anterior and middle cerebral arteries. Minimal reconstitution was via the posterior communicating artery.

Lessons for the Clinician

- The most common mechanisms of injury for carotid artery dissection (CAD) are direct blows to the head or neck, hyperextension of the neck, and intraoral injury.
- The most common presenting symptoms are focal neurologic deficits consistent with stroke, such as aphasia, hemiparesis, ataxia, facial palsy, and somnolence.
- CAD is diagnosed using angiography, whether computed tomographic angiography or conventional.
- Treatment for CAD is antiplatelet therapy or anticoagulation. Surgery is reserved for progressive or recurrent symptoms.
- If there is a high suspicion of CAD, the provider should immediately refer the patient for imaging at a hospital with neurosurgery available because early diagnosis and therapy can prevent the occurrence or recurrence of stroke.

ACKNOWLEDGMENT

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Index of Suspicion

2 A 10-year-old Boy Who Refuses to Walk

Monaliza S. Evangelista, MD,* Nikita Khetan, MD,† Emma A. Omoruyi, MD*

*Division of Community and General Pediatrics, †Department of Pediatrics, McGovern Medical School at The University of Texas Health Science Center at Houston, Houston, TX

PRESENTATION

A 10-year-old boy with a history of anomalous left coronary artery repaired during infancy presents to the hospital due to worsening right lower extremity pain for the past 3 weeks. The patient had residual mitral valve prolapse and moderate mitral valve regurgitation, moderate pulmonic regurgitation, and left atrial dilatation after the initial repair of his congenital heart disease. At the start of his symptoms, he was able to walk and run, but in the past few days, the pain has worsened. He now refuses to run and tries to walk slowly only when prompted to walk. His mother is also concerned that he has lost weight since the start of the pain, with accompanying anorexia. The family denies any history of trauma. He takes aspirin daily due to a history of congenital heart disease. Three weeks ago, before the pain started, his mother brought him to the hospital for evaluation of a fever. He was diagnosed as having a viral infection and was discharged. Since then his mother recalls intermittent episodes when he felt warm but on checking his temperature, it was normal.

During his evaluation in the emergency department this time, he is noted to have a temperature of 102.8°F (39.3°C) and tachycardia to 125 beats/min. Laboratory values are significant for elevated erythrocyte sedimentation rate and C-reactive protein level, a normal white blood cell count but with a neutrophilic predominance, and anemia (hemoglobin level, 9.3 g/dL [93 g/L]). An imaging study, suggested by an orthopedic surgery colleague, reveals the diagnosis.

DISCUSSION

A magnetic resonance image of the boy's lower extremity was concerning for an arterial thrombosis in the right lower extremity (Fig 1). He was admitted to the general pediatric service for further evaluation. On admission, his physical examination was significant for a child who was lying in bed in no acute distress but did not engage with discussion. Cardiac examination revealed a loud grade 6/6 systolic murmur heard best at the apex. His lower extremities were of the same size, and no overlying erythema or edema was observed. However, he had significant pain to palpation of the right posterior distal lower extremity. No palpable cord was noted, but the dorsalis pedis pulse was 1+ compared with 2+ on the contralateral lower extremity. Because of his clinical history and examination concerning for an embolic phenomenon, endocarditis was suspected. Blood cultures were obtained, and broad spectrum antibiotic drug therapy was initiated.

AUTHOR DISCLOSURE Drs Evangelista, Khetan, and Omoruyi have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

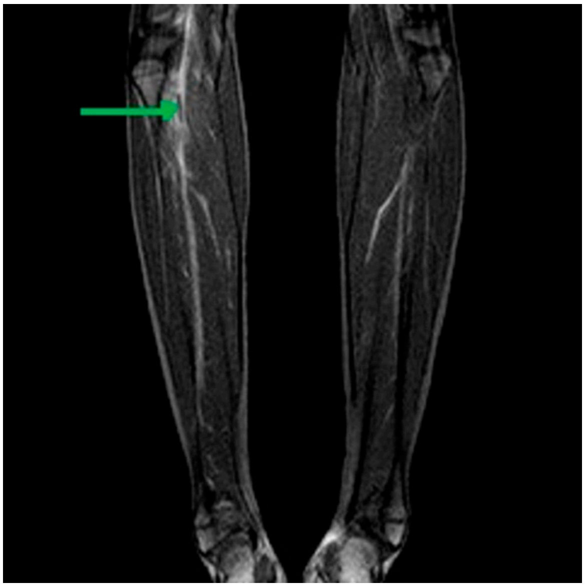

Figure 1. Postcontrast T1-weighted magnetic resonance image of the bilateral tibia and fibula depicting a 2-cm arterial occlusion (green arrow) of the right tibioperoneal trunk. Note the change in signal from bright to dark back to bright correlating to obstruction and then reconstitution of flow.

The patient's blood cultures grew α-hemolytic *Streptococcus* within 24 hours. A 2-dimensional echocardiogram showed vegetations on the mitral valve, with partial rupture (Fig 2). Magnetic resonance imaging of the brain and foot showed evidence of septic emboli, and ophthalmologic examination revealed "cotton wool" spots and areas concerning for septic emboli. Based on these findings, the patient was treated with intravenous penicillin for 6 weeks and gentamicin for the first 2 weeks. An echocardiogram before completion of treatment showed that the vegetation on the anterior mitral valve leaflet was slightly increased in size and now pedunculated, making the risk of embolization greater. Therefore, antibiotic drug therapy was extended for an additional 2 weeks to complete a total of 8 weeks. With the extension in therapy, the size of the vegetation decreased and the patient remained stable.

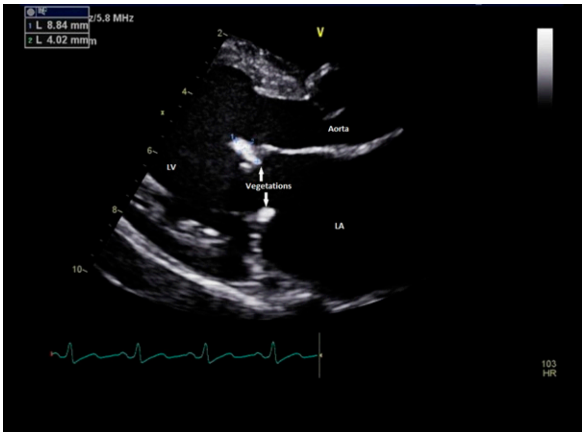

Figure 2. Echocardiogram showing vegetations attached to the mitral valve.
LA=left atrium; LV=left ventricle.

Four weeks after hospital discharge, the patient was admitted for elective posterior mitral valve annuloplasty and anterior mitral valve leaflet vegetation removal. He tolerated the procedure well and was discharged. However, subsequent echocardiograms over the following 3 months showed recurrence of mitral valve regurgitation; therefore, the patient underwent a full mitral valve repair 3 months later. The patient tolerated that procedure well and was discharged in stable condition. Subsequent follow-up in the outpatient clinic has continued, and the patient remains stable.

The Condition

Bacterial endocarditis is an infection of the endothelial surface of the heart. Across 37 US children's hospitals, a little more than 1,000 children were admitted for infective endocarditis, and 68% of these patients had underlying congenital heart disease. (1) Children with congenital heart disease are at higher risk for endocarditis than the general pediatric population. Flow in a damaged valve leads to turbulence, which, in turn, damages the endothelium, resulting in formation of a thrombotic endocardial lesion. This thrombotic lesion is susceptible to becoming a nidus of infection during a transient bacteremia, and the turbulent blood flow through the damaged valve results in embolization to almost any part of the body.

The clinical hallmarks of endocarditis include bacteremia, cardiac invasion by microbes, and peripheral embolization. Pediatric endocarditis is further classified into subacute and acute processes. The subacute process is hallmarked by a protracted clinical course of low-grade fever, general malaise, sweating, and weight loss. Patients with acute endocarditis have a rapid illness, high fever, and very ill appearance. The most common organisms associated with pediatric endocarditis include *Staphylococcus* and *Streptococcus* species. (2) However, *Staphylococcus aureus* is the most common causative pathogen and is associated with the highest mortality rate seen in acute endocarditis especially related to systemic emboli. (2)

Most commonly, the diagnosis of endocarditis is made by following the revised Duke criteria (Table 1). (2)(3) The revised Duke criteria require the presence of 1 of 2 pathologic criteria or certain combinations of clinical results divided into major and minor findings. (2)(3) The pathologic

TABLE 1. Revised Duke Criteria for the Diagnosis of Endocarditis

MAJOR DIAGNOSTIC CRITERIA	MINOR DIAGNOSTIC CRITERIA
Positive blood culture for typical infective endocarditis organisms from 2 separate blood cultures or 2 positive cultures from samples drawn >12 h apart, or 3 or a majority of 4 separate cultures of blood (first and last sample drawn 1 h apart)	Predisposing heart condition
Echocardiogram with oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomical explanation, or abscess, or new partial dehiscence of prosthetic valve or new valvular regurgitation	Temperature >100.4°F (>38°C)
Single positive blood culture for *Coxiella burnetii* or anti–phase 1 immunoglobulin G antibody titer >1:800	Vascular phenomena: arterial emboli, pulmonary infarcts, mycotic aneurysms, intracranial bleed, conjunctival hemorrhages, Janeway lesions Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor Microbiologic evidence: positive blood culture but does not meet a major criterion or serologic evidence of active infection with organism consistent with endocarditis (excluding coagulase-negative *Aggregatibacter* staph, and other common contaminants)

criteria include direct evidence of endocarditis based on histologic findings and positive Gram-stain or culture of specimens obtained from surgery or autopsy. The clinical diagnosis requires the presence of 2 major and 0 minor criteria, 1 major and 3 minor criteria, or 0 major and 5 minor criteria.

Embolization, a known complication of bacterial endocarditis, has been described in 11% to 44% of patients, and one-third of these patients have embolization to the peripheral vasculature. (4) As was seen in our patient, large (>10 mm), left-sided, and pedunculated vegetations are more likely to embolize. (4) Complications of embolization to the peripheral vasculature typically present with worsening pain at the site and fever.

Differential Diagnosis

In a child who presents with leg pain, the differential diagnosis can be broad and includes fracture due to accidental or nonaccidental trauma, musculoskeletal strain/sprain, infection, myositis, malignancy, embolic phenomenon, and thrombosis.

Treatment

The management of bacterial endocarditis is highly dependent on the underlying causative microbial agent. Therefore, it is extremely important to obtain blood cultures when the diagnosis is in question so that empirical therapy may be initiated and then tailored based on several factors, including the causative agent, previous antibiotic exposure, route of infection, whether the infected valve is native or prosthetic, and whether the infectious process is subacute or acute. (5) In many cases, consultation with an infectious disease specialist is recommended.

Treatment of endocarditis requires the use of antibiotic agents specifically targeting bacterial pathogens (Table 2) and generally requires inpatient treatment. Culture-negative endocarditis occurs rarely in children and is usually diagnosed only when there is clinical or echocardiographic evidence and suspicion of bacterial endocarditis but persistently negative blood cultures. (5)

During antibiotic drug treatment, the patient's clinical course should be monitored with antimicrobial levels, echocardiography, and repeated blood cultures. If a patient is receiving gentamicin or vancomycin, levels of these antimicrobial agents should be checked at least once each week. (5) Repeated echocardiography may be needed to assess for changes in vegetations and to evaluate valvular and myocardial function. (3)(6) Furthermore, repeated blood cultures may be needed to demonstrate eradication of the causative agent and if symptoms recur.

In patients who fail medical therapy and who continue to have persistent vegetations despite antibiotic drug therapy, surgical intervention may be considered. The most common reasons for surgical intervention are congestive heart failure, progressive valvular dysfunction, and embolic phenomena. (3)(5)

When bacterial endocarditis is recognized and treated early, patients typically do well. However, the overall

TABLE 2. Antibiotic Regimens for the Treatment of Endocarditis Based on Causative Organism (4)

CAUSATIVE AGENT	ANTIBIOTIC REGIMEN
Viridans group streptococci *Streptococcus bovis*	Penicillin G for 4 wk OR Ampicillin for 4 wk OR Ceftriaxone for 4 wk
Enterococci	Penicillin G for 4–6 wk OR Ampicillin + gentamicin for 4–6 wk OR Ceftriaxone + ampicillin for 6 wk
Staphylococci	Methicillin sensitive Native valve: Nafcillin/oxacillin for 4–6 wk OR Cefazolin for 4–6 wk Prosthetic valve: Nafcillin/oxacillin for 6 wk OR Cefazolin + rifampin for 6 wk + gentamicin for first 2 wk Methicillin resistant Native valve: Vancomycin for 6 wk Prosthetic valve: Vancomycin for 6 wk + rifampin for 6 wk + gentamicin for first 2 wk
Gram-negative organisms (HACEK [*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens, Kingella*])	Ceftriaxone for 4 wk OR Cefotaxime for 4 wk OR Ampicillin + gentamicin for 4 wk

mortality rate is approximately 5%; effective and adequate treatment is key. (2) Most children with bacterial endocarditis have an identifiable risk factor such as preexisting heart disease, prematurity, or an underlying palliative shunt or prostheses. In these patients in particular, the risk of complications and the rates of morbidity and mortality are higher. Inadequate or delayed treatment, particularly, in high-risk patients, can lead to life-threatening complications such as heart failure, extension of the infection resulting in arrhythmias and heart block, or metastatic infection (such as osteomyelitis, pneumonia, or distal abscesses), as demonstrated in this patient. (2)

Lessons for the Clinician

- Bacterial endocarditis is a potentially life-threatening disease commonly seen in patients with an underlying risk factor, such as preexisting heart disease or an indwelling catheter.
- Due to the increased survival rate of children with congenital heart disease and the increased use of central venous catheters, the incidence of bacterial endocarditis has increased during the past 3 decades.
- The clinical presentation of bacterial endocarditis is highly variable and may include nonspecific complaints such as low-grade fevers, fatigue, arthralgias, and myalgias.
- The treatment for bacterial endocarditis should be guided by the causative agent identified on blood culture, the route of infection, the cardiac history (prosthetic versus native valve), and the presentation of infection (acute versus subacute).

References for this article are at http://pedsinreview.aappublications.org/content/40/7/362.

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Case 2: A 10-year-old Boy Who Refuses to Walk

Monaliza S. Evangelista, Nikita Khetan and Emma A. Omoruyi

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Index of Suspicion

3 Anisocoria in a 5-year old Girl

William McEachern, MD,* Alice Walz, MD,[†] Keerti Dantuluri, MD,[‡]
Daniel Dulek, MD,[‡] Kristina Betters, MD[†]

*Department of Pediatrics, [†]Division of Pediatric Critical Care Medicine, and [‡]Division of Pediatric Infectious Diseases, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN

PRESENTATION

A previously healthy 5-year-old girl presents to the emergency department with a chief complaint of persistent left-sided neck swelling with new-onset headache, odynophagia, and pupillary asymmetry. She has developed the left neck swelling over the course of the past month. She is initially evaluated with lateral neck ultrasonography as an outpatient; this demonstrates enlarged cervical lymph nodes without fluid collection or abscess. She completes a course of clindamycin for presumed cervical lymphadenitis and is subsequently treated with a course of amoxicillin–clavulanic acid after the first course of antibiotic agents fails to improve her symptoms. Parents state that they have not appreciated a significant change in the degree of neck swelling after the 2 antibiotic drug therapy courses, and the girl endorses a major increase in neck pain and headache last night that is unresponsive to acetaminophen or ibuprofen, both of which had previously been alleviating her pain. She is also noted to have pupillary asymmetry for the previous 2 days.

She has not had fevers, vomiting, seizures, weight loss, or changes in speech or vision. She remains at her neurologic baseline. There is no history of trauma or recent surgery. She is fully immunized and has no known allergies.

In the emergency department she is well-appearing, afebrile, and with age-appropriate vital signs. She is noted to have partial left-sided ptosis and miosis, as well as tender, palpable left-sided cervical lymphadenopathy (Fig 1).

DISCUSSION

This girl's clinical presentation is consistent with Horner syndrome, also known as oculosympathetic palsy, which is caused by a disruption of the ocular sympathetic supply to the eyelids and pupils and may occur anywhere along the 3-neuron pathway between the hypothalamus and the orbit. The etiology of Horner syndrome is varied and age dependent. (1) A retrospective review of 73 pediatric patients with Horner syndrome found that 42% were congenital in nature (including birth trauma), 42% were acquired after a surgical procedure, and 15% were acquired without surgical intervention. In the 15% of cases acquired without surgical intervention, etiologies included neuroblastoma, trauma,

AUTHOR DISCLOSURE Drs McEachern, Walz, Dantuluri, Dulek, and Betters have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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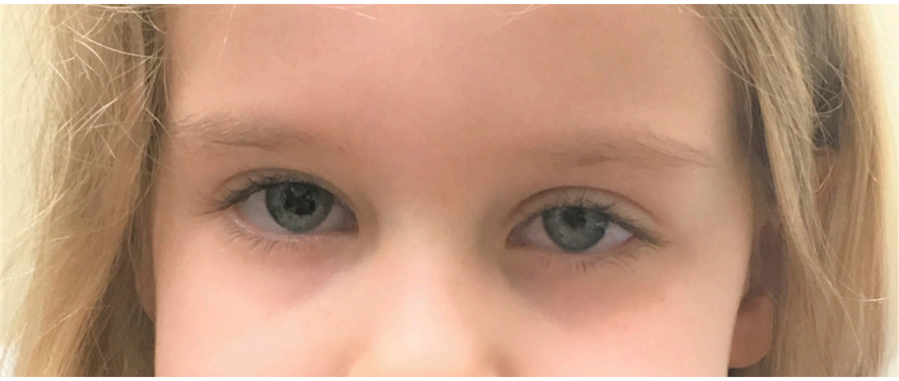

Figure 1. Left-sided ptosis and miosis.

rhabdomyosarcoma, brainstem vascular malformation, disseminated sclerosis, and other causes not determined. (1)

Our patient's initial laboratory work revealed a white blood cell count of 9,500/μL (9.5×10^9/L) with 68% neutrophils, a C-reactive protein level of 1.1 mg/L (10.5 nmol/L) (of note, her initial outpatient C-reactive protein level, 19 days before emergency department presentation, was 68 mg/L [647.6 nmol/L]), and an erythrocyte sedimentation rate of 23 mm/hr. She had a negative rapid mononucleosis screen. Her coagulation profile was normal. A contrasted computed tomographic scan of the head was obtained, which revealed a lobulated enhancing left cervical mass that was suspicious for a pseudoaneurysm abutting the anterior aspect of the distal left cervical internal carotid artery (ICA) at the level of the skull base. Magnetic resonance angiography of the head and neck confirmed the diagnosis of a large, partially thrombosed pseudoaneurysm of the left ICA (1.9 × 4.0 × 4.0 cm), with moderate stenosis of the left cervical ICA along the posterolateral aspect of the pseudoaneurysm.

The Condition

Pseudoaneurysms in the ICA are rare in the pediatric population and most commonly result from traumatic injury to the carotid artery. Traumatic causes include external trauma or iatrogenic injury to the vessel during surgical procedures. Pseudoaneurysms in the ICA can also occur as a rare complication of a deep neck space infection, usually developing a few days to 2 months after the initial infection. (2) However, since the widespread use of antibiotic drugs for the treatment of otolaryngologic infections, the frequency of this complication has significantly decreased. (3)

The pathophysiology of pseudoaneurysm development after infection is not completely understood, but it is thought to be caused by the introduction of infection from pharyngeal, tonsillar, peritonsillar, or lymphatic channels. (2) A septic focus may cause adjacent arteritis and a weakened arterial wall, leading to aneurysmal dilation. (4) Pediatric deep neck space infections are usually due to abscesses or lymphadenitis and, less commonly, bacterial endocarditis. The most common microbiological causes of cervical lymphadenitis include *Staphylococcus aureus*, streptococcal species, anaerobic organisms, and viruses (Epstein-Barr virus, cytomegalovirus, and adenovirus). (5)

Diagnosis

Clinical signs suggestive of pseudoaneurysm are Horner syndrome, paralysis of cranial nerves, a pulsating and tender neck mass, lack of resolution of lymphadenitis symptoms after antibiotic drug therapy, or stroke due to embolization of thrombus from within the pseudoaneurysm. Larger pseudoaneurysms can compress the glossopharyngeal nerve, leading to dysphagia, odynophagia, and retro-orbital headache. (6)

The diagnosis of ICA pseudoaneurysm is usually made by ultrasonography of the neck or by computed tomographic scan. Additional vascular imaging using computed tomography angiography or magnetic resonance imaging angiography is helpful to delineate the anatomy, the extent of pseudoaneurysm dilation, and its relationship to surrounding structures before initiating vascular repair.

Management

Patients with ICA pseudoaneurysm require urgent management because they are at risk for rapid decompensation secondary to hemorrhage, airway compromise, and stroke. (7) The aim of management is to restore the continuity of the artery by separating the pseudoaneurysm from the carotid circulation. Historically, this has been accomplished by surgical ligation or coil sacrifice of the vessel. However, more recently, a strategy to reestablish arterial continuity through endovascular embolization of the pseudoaneurysm and stenting of the ICA has been successful. (2)(6)(7) If

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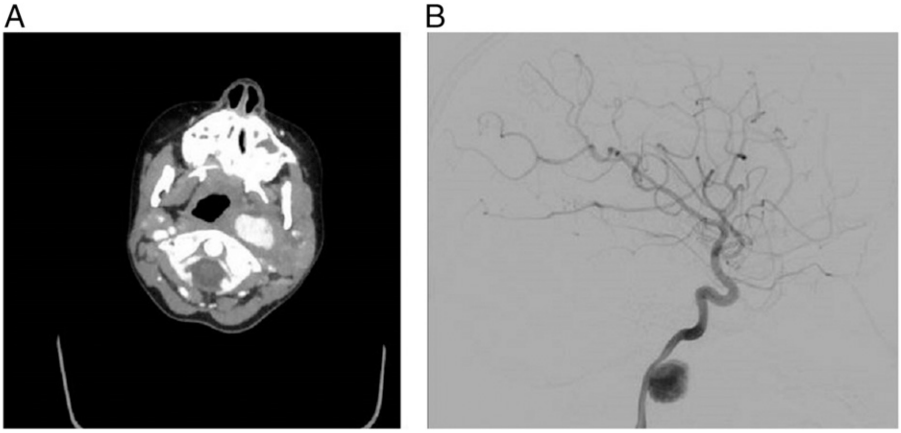

Figure 2. A. Contrasted computed tomographic scan showing a lobulated enhancing mass concerning for pseudoaneurysm at the level of the skull base. B. Angiogram showing left internal carotid artery pseudoaneurysm with moderate stenosis of the internal carotid artery.

ligation of the vessel is the planned mode of intervention, it is imperative to first ensure that there is an intact collateral blood supply to the anterior circulation.

Patient Course

Our patient was admitted to the PICU for serial neurologic checks, and both the pediatric neurosurgery and infectious disease teams were consulted. Interventional radiology–guided biopsies of a necrotic lymph node adjacent to the pseudoaneurysm as well as the left parotid gland (as the pseudoaneurysm involved its deep space) were obtained and sent for culture. Aspirin and clopidogrel prophylaxis were initiated for the pseudoaneurysm, and empirical ceftriaxone was started after lymph node biopsy.

Blood cultures and bacterial, fungal, and acid-fast bacillus cultures from the biopsied lymph node were negative. She had no evidence of acute bacterial endocarditis or endovascular infection. She had recently visited a zoo, so less common causes of lymphadenitis were considered, including *Brucella* species, *Francisella tularensis*, and *Yersina pesitis*; however, she denied contact with any animals. *Coxiella* titers were obtained given *Coxiella*'s ability to cause culture-negative endocarditis, and results were negative. Given her residence in Tennessee, *Histoplasma capsulatum* was also considered, but she had no exposure to chicken coops or construction. Tuberculosis screening was negative. Despite no known recent exposure to cats or kittens on history, she reported enjoying playing with cats. Her *Bartonella* immunoglobulin G titer was 1:256 (normal, <1:64); however, serum *Bartonella* by polymerase chain reaction was negative. Such findings were suggestive of a past or subacute infection, versus acute infection, and were consistent with her initial symptoms occurring 1 month before presentation. There are no previously published case reports of pseudoaneurysm caused by *Bartonella* lymphadenitis; however, based on the pathophysiology of cervical ICA pseudoaneurysm secondary to deep neck infections, we believe that this underlying *Bartonella* infection was the cause of adjacent arterial inflammation, leading to pseudoaneurysm formation.

Diagnostic angiography was performed, which confirmed the ICA pseudoaneurysm (Fig 2), with significant narrowing of the ICA. Collateral blood flow to the anterior circulation was intact, and the patient underwent successful endovascular embolization of the pseudoaneurysm with reconstruction of the ICA by placement of an endovascular stent. Follow-up angiography demonstrated normal flow through the carotid artery as well as successful occlusion of the pseudoaneurysm. She was maintained on clopidogrel and aspirin therapy and was discharged on an extended course of antibacterial drug therapy with oral cefdinir. On follow-up 1 month after her procedure, she was noted to have continued Horner syndrome but resolution of neck swelling and pain. Long-term anticoagulation with aspirin and clopidogrel was continued, with plans for repeated angiography 6 months after arterial stent placement.

Lessons for the Clinician

- Consider early referral to an infectious disease specialist for evaluation of a patient with presumed lymphadenitis who is not improving with an appropriate antibiotic drug course.
- Be suspicious of internal carotid artery pseudoaneurysm in a patient with Horner syndrome.
- Patients with internal carotid artery pseudoaneurysm require urgent management because they are at risk for hemorrhage, stroke, and airway compromise.

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Case 3: Anisocoria in a 5-year old Girl

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4 Fever, Vomiting, and Abdominal Pain in a 23-month-old Girl

Brenna Keane, DO,* Paul Whalen, MD*†

*Carilion Children's, Carilion Roanoke Memorial Hospital, Roanoke, VA

†Virginia Tech Carilion School of Medicine, Roanoke, VA

PRESENTATION

A previously healthy 23-month-old girl presents to the emergency department with a 1-week history of fever (maximum temperature, 104.6°F [40.3°C]), vomiting, and abdominal pain. Vomiting occurs 3 to 4 times daily, and emesis is described as nonbloody and nonbilious. Her parents report that the patient has also been intermittently crying out in pain, clutching her belly. Associated symptoms include fussiness, decreased oral intake, and decreased urine output.

On initial physical examination the girl is sleeping. Her temperature is 98.6°F (37.0°C), heart rate is 137 beats/min, respiratory rate is 30 breaths/min, blood pressure is 104/69 mm Hg, and oxygen saturation is 100% on room air. She has dry lips, a mildly distended abdomen, and obvious facial grimacing (during sleep) with generalized light palpation of all 4 abdominal quadrants. Screening laboratory tests are significant for a white blood cell (WBC) count of 16,200/μL (16.2×10^9/L) (50% neutrophils, 29% lymphocytes, 11% monocytes, 6% bands) and positive nitrites, positive WBC esterase, 10 to 25 WBCs, and bacteria on urinalysis.

An acute abdominal series (Fig 1) shows a "soft-tissue density in the right lower quadrant, likely stool-filled colon." Due to clinical suspicion for intussusception, abdominal ultrasonography (Fig 2) is performed, demonstrating a "nonperistalsing fecal ball-like structure in the right lower quadrant" but no target sign. Water-soluble contrast enema is performed, which shows no evidence of intussusception. Pediatric surgery determines no need for surgical intervention, and the patient is admitted by the pediatrics team for intravenous rehydration and treatment of possible pyelonephritis. Further evaluation reveals the correct diagnosis.

DISCUSSION

After admission, the patient continued to have abdominal pain, malaise, and fussiness. Of increasing concern was the persistence of abdominal distention and diffuse guarding on physical examination. Repeated abdominal ultrasonography was again inconclusive, so a CT scan of the abdomen/pelvis (Fig 3) was obtained for further evaluation of the appendix. CT revealed perforated appendicitis with a forming abscess and extravasation of contrast into the abscess, dilated loops of

AUTHOR DISCLOSURE Drs Keane and Whalen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

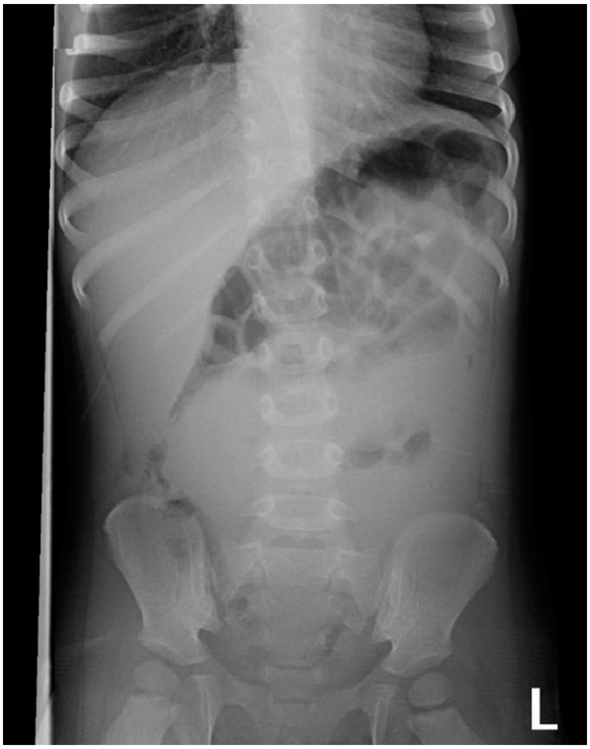

Figure 1. Acute abdominal series.

small bowel, and multiple air-fluid levels. The girl subsequently underwent laparoscopic appendectomy with surgical drainage of abdominal abscess. Pathology was consistent with gangrenous and perforated appendix. She received 1 week of intravenous antibiotic drug therapy and was discharged on broad spectrum antibiotics. She fortunately experienced a full recovery.

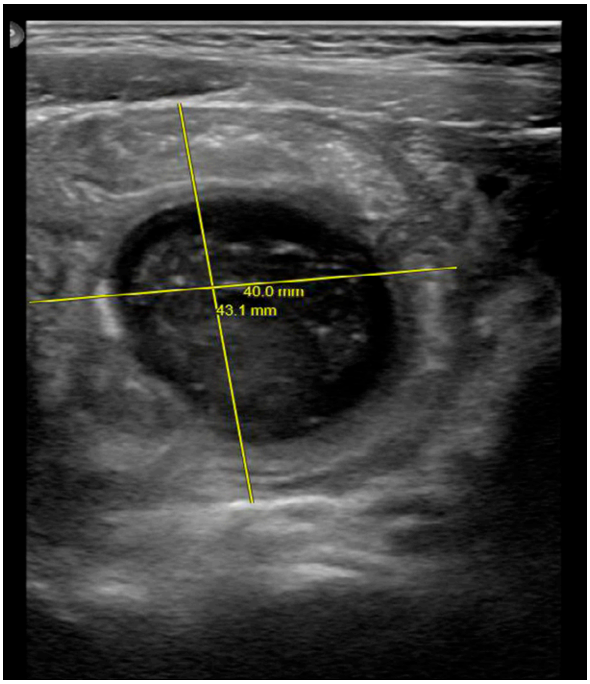

Figure 2. Abdominal ultrasonographic image, limited.

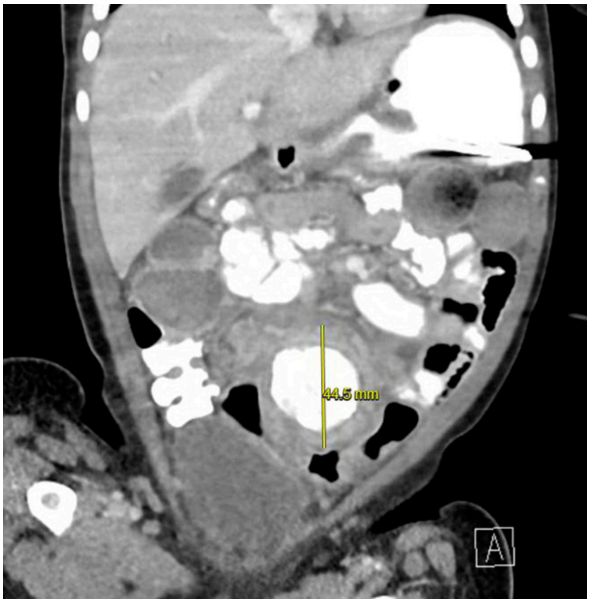

Figure 3. Computed tomographic scan of the abdomen/pelvis with contrast.

This case highlights the importance of repeated physical examinations and the need for reevaluation when a patient does not improve as expected. Furthermore, it demonstrates the advantages of interdisciplinary cooperation and communication between medical teams. This patient was initially seen by pediatric surgery but was admitted by pediatrics and then cared for by both services. She underwent an extensive evaluation, including an arguably unnecessary water-soluble contrast study and inconclusive abdominal ultrasonography twice, before a CT scan was diagnostic.

The Condition

Appendicitis, although very common in the pediatric population as a whole, is rare in children younger than 2 years. In this young age group, the diagnosis of appendicitis is especially challenging because presentation differs and symptoms cannot be reliably described.

In the gastrointestinal tract, lymphatic tissue proliferation increases with increasing age and peaks in late adolescence. There is, therefore, a greater likelihood for appendiceal luminal obstruction and subsequent development of appendicitis in the teenage years. When infants and toddlers do get appendicitis, however, they are more likely to present with diffuse abdominal tenderness and peritonitis, not localized right lower quadrant tenderness as classically described.

In children younger than 2 years, there is frequently a delay in diagnosis, partially explained by the fact that young children lack the communication skills necessary to accurately describe their symptoms. Initial misdiagnosis rates are also very high. As was well-demonstrated in this case, appendicitis can be associated with pyuria and bacteriuria, leading to an incorrect diagnosis of urinary tract infection. In a young child with persistent abdominal pain and urinary signs of infection, appendicitis should, therefore, be considered. In general, appendicitis in this unique and vulnerable population is more likely to be complicated and is associated with increased morbidity.

Lessons for the Clinician

- In children younger than 2 years, appendicitis is associated with atypical presentation, delayed diagnosis, complications, and increased morbidity.
- Appendicitis can be associated with pyuria and bacteriuria, leading to an incorrect diagnosis of urinary tract infection.
- Appendicitis should be included in the differential diagnosis of a young child with persistent abdominal pain and urinary signs of infection.

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Suggested Readings

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Case 4: Fever, Vomiting, and Abdominal Pain in a 23-month-old Girl

Brenna Keane and Paul Whalen

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Case 4: Fever, Vomiting, and Abdominal Pain in a 23-month-old Girl

Brenna Keane and Paul Whalen

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in Brief

Applying Big Data to Pediatric Care

Benson S. Hsu, MD, MBA,*†‡ Justin P. Smith, PhD,* Emily R. Griese, PhD*†‡
*Sanford Health, Sioux Falls, SD
†Department of Pediatrics, University of South Dakota Sanford School of Medicine, Vermillion, SD
‡Sanford Research, Sioux Falls, SD

At the forefront of health-care innovation is the ability to harness the power and potential of *big data*, commonly described as data with 3 key components: volume, variety, and velocity. Health-care gathers one of the largest and most diverse data sets, with some health systems harboring nearly 2 decades worth of electronic medical records (EMRs). Big data, however, is more than just a large volume of data (often a terabyte or even petabyte in size); it also intentionally merges a variety of data sources. In health-care, this may comprise traditional EMR data combined with data sets such as census and geospatial data. Coupled with velocity, ie, the capacity to manage rapidly generated data (ie, through personal health monitors), big data provides a new dimension to health-care, one with the possibility to transform the way patient care is provided. This *In Brief* aims to explore advances in using big data, the possibilities that exist with its application, and its relevance to health-care professionals.

THE DATA

Health-care data are messy. Considering the number of data collectors in a clinic or hospital or health-care system, from nurses to physicians to registrars to coders, and the various data captures, from physician notes to pathology reports to coding abstractions, the potential for interpretation and recorder biases are numerous, resulting in the familiar adage of "garbage in, garbage out." Combining non–health-care data sources with traditional health-care data is further fraught with concerns given the often-lacking data governance across these data sets. For instance, inconsistent data definitions can result in a multitude of ways to define quality. This can exist even in disparate data elements, ie, those requiring a predetermined set answer or response. For example, readmissions rates may be calculated differently both within and across health-care systems, depending on the variability of defining admission types, clouding the ability to establish actionable or comparable insights. Furthermore, significant portions of health-care data reside in unstructured formats (non-predetermined set of answers or responses), such as provider notes. Without adoption of advanced data science techniques such as natural language processing, these unstructured data will remain untapped.

Data scientists in health-care and other industries have begun to break down the barriers of big data through standardizing data terms and extracting unstructured data. Data quality and management tools are becoming ubiquitous throughout the data science world, tying down specific approaches to normalize health-care data at the practice, clinic, hospital, or health system level. Natural language processing, still in its infancy, is already showing promise in translating unstructured data in patient encounter notes into

AUTHOR DISCLOSURE Drs Hsu, Smith, and Griese have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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THE POSSIBILITIES

Big data opens new doors, with the potential for fast-paced, innovative change in health-care practice at the bedside. Given the significant lag in implementing research advancements, taking nearly 17 years to turn original research to the benefit of patient care, with only 14% of total research ever being used to benefit patient care, the application of big data to health-care provides a new pipeline for rapid advancement and innovation. Data scientists are continuously developing novel algorithms of care that incorporate machine learning and other analytical techniques to be used in real-time at the bedside with streaming data. For example, an algorithm can readily identify the relationships among seasonal weather patterns, triggers in community social media data regarding missed school days, external data reported to public health sources, and acute changes in vital signs in a clinic. In doing so, this algorithm can alarm a pediatrician to a high pretest probability of a diagnosis of influenza closer to the start of the season versus waiting for lagging surveillance data.

With the anticipated shift of care from the traditional fee-for-service model to one based on maximizing quality while minimizing costs, big data can drive specific provider behavior to improve care delivery focused on achieving this goal. For example, through big data, exploration of the relationships between societal indicators such as socioeconomic movements against various methods to improve diabetes management compliance, pediatricians may be able to identify novel levers to decrease avoidable and costly admissions for diabetic ketoacidosis. Similarly, big data has the potential to help pediatricians implement the most optimal obesity care plan through tracking biometric markers (weight, blood sugar, daily steps) and relating this to patient-specific information, including distance from clinics, food purchases, prescription adherence, exercise patterns, and even social media activity. Having a global understanding of the patient through a constant stream of data can decrease the morbidity and mortality of many chronic conditions, such as diabetes and obesity.

The application of big data to health-care must proceed with caution. Privacy concerns, data ownership complexities, and discriminatory bias still cloud the widespread adoption of big data in clinical care. Given enough data points, previously deidentified patients can be reidentified through complex manipulations of data. Also, the concept of data ownership (which party—patient or provider or payer—holds the rights) remains unclear, with the government giving no guidance to this topic to date. Last, discriminatory bias can be introduced by using geographic markers such as zip codes as these can easily serve as racial or socioeconomic proxies in analysis. Regulatory and ethical guidance need to be further strengthened before widespread integration of big data into clinical care.

Importantly, pediatricians must guide the development of insights driven from big data. The influx of big data without the expertise of a practitioner becomes, at best, a mathematical equation. At worst, the analytical outcome may have a seemingly appropriate benefit but result in a negative effect on population health. It is foreseeable that some algorithms, developed using big data, may not benefit the patient at hand or may have an unforeseen negative impact. For instance, a recent paper from *The BMJ* revealed that working to decrease admissions from the emergency department, a measure of utilization, increased the rates of early death.

Pediatricians on the front line of care must be involved to ensure that big data algorithms have a clinically relevant effect on improving the health of their patients. For some, this involvement will be through the education of their trainees on algorithm development and use. For some, this will come purely from the standardization of data collection through the EMRs. For some, this will be through formal roles, such as being a chief analytics officer in driving the strategies for clinical use of big data. Last, for most, this will be through the application of the products of big data, whether in direct patient care clinical algorithms or through embedded clinical support alerts from the EMR. Regardless, it is incumbent on all types of pediatricians, from trainees, to academic clinicians, to practitioners in the community, to augment the application of big data and to not blindly follow it. With this caution in mind, it is evident that the inevitable avalanche of big data algorithms will improve not only the way we care for our patients but also our communities.

COMMENT: The implementation of big data into health-care and clinical reasoning is an exciting venture in pediatrics. The example given about identifying influenza disease early in the community before epidemiologic surveillance is just 1 example of the usefulness. Capitalizing on the collation of data from thousands of patients could lead to earlier identification of clinical problems and potential solutions. For big data to be successfully incorporated into health-care, attention must be given to incorporating a multidisciplinary approach and include the frontline providers to ensure that the use is meaningful and valuable to patients. I find this concept so exciting, and it brings with it the possibility of transforming health-care at both the individual patient and population levels.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

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Varicella Zoster Virus

Robyn J. Blair, MD
Department of Pediatrics, Stony Brook University School of Medicine, Stony Brook, NY

Varicella zoster virus (VZV), human herpesvirus 3, is a highly contagious virus found worldwide. Humans are the only known reservoir. Transmission is via respiratory droplets, aerosolized vesicular contents, or direct contact with skin lesions. After infection, VZV becomes latent in sensory ganglia, with reactivation possible even decades later.

Primary infection with VZV results in varicella (chickenpox), which is typically seen in school-age children in temperate climates in late winter and early spring. Before the varicella vaccine, there were approximately 4 million cases of varicella and 100 varicella-related deaths in the United States per year, whereas after vaccination, the incidence has declined 97%, with no reported pediatric deaths since 2010. Varicella disease presents as a diffuse, pruritic, vesicular rash, with fever and malaise appearing just before or on the day of the rash. The contagious period begins 1 to 2 days before the appearance of the rash and continues until all lesions are crusted, an average of 7 days. The incubation period lasts from 10 to 21 days, with an average of 14 to 16 days. Lesions begin as macules, progressing to papules, then vesicles. Initially, lesions are 2- to 4-mm, thin-walled, irregular vesicles with clear fluid over an erythematous base, classically described as "dewdrops on a rose petal." The rash usually starts on the head, trunk, and then extremities but can appear anywhere, including mucous membranes. As they resolve, vesicles become umbilicated, fill with cloudy fluid, and develop crust. Lesions in varying stages of healing is a hallmark feature. Healthy, unvaccinated children have an average of 200 to 500 lesions. Lesions typically do not scar unless they become infected or excoriated. Once all lesions have crusted, children may return to school.

The most common complication of VZV in children is secondary bacterial skin infection with *Staphylococcus* or *Streptococcus*. Because infection with varicella usually includes a viremia, dissemination to other organs can occur. Acute cerebellar ataxia is the most common extracutaneous complication. Encephalitis can occur and may lead to seizure and coma. Pneumonia after varicella can be due to viruses but is more commonly bacterial in children less than 12 months old. Additional, but more rare, complications include aseptic meningitis, Guillain-Barré syndrome, hepatitis, myocarditis, hemorrhagic varicella, transverse myelitis, uveitis, and iritis. Immunocompromised children are at greater risk for severe disease from VZV as well as severe complications and even death.

Primary maternal VZV infection during the first or early second trimester of pregnancy results in congenital varicella syndrome in up to 25% of cases. Clinically, affected babies can have intrauterine growth retardation, contracted scarring, hypoplastic limbs and digits, and central nervous system abnormalities such as microcephaly, cortical atrophy, mental retardation, and hydrocephalus.

Reactivation of VZV manifests as herpes zoster (shingles), a painful vesicular eruption typically unilateral along a dermatomal distribution most commonly on

AUTHOR DISCLOSURE Dr Blair has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Global Varicella Vaccine Effectiveness: A Meta-analysis. Marin M, Marti M, Kambhampati A, et al. *Pediatrics.* 2016;137(3):e20153741

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the trunk or involving the fifth cranial nerve. The rash begins as macules and papules, progressing to vesicles that develop crust and resolve. Once lesions are crusted, they are no longer contagious. Pain and paresthesia usually occur several days before the appearance of the rash. The average rash duration is 10 days. Although rare in children, postherpetic neuralgia may continue for months after rash resolution. If lesions can be covered, patients can return to school.

Treatment for primary VZV is supportive, with antipyretics, fluid, and control of itching. Aspirin should be avoided due to the risk of Reye syndrome. Antiviral therapy with acyclovir, an acyclic nucleoside analog, is generally not used for healthy children younger than 12 years. However, in patients with severe VZV infection in a high-risk group (individuals with chronic cutaneous or pulmonary disorders, those receiving long-term aspirin or corticosteroid therapy, and unvaccinated children older than 12 years), oral acyclovir may be considered. Initiation of acyclovir treatment within 24 hours of rash onset provides the greatest benefit. Immunocompromised patients with VZV infection should be treated with intravenous acyclovir within 24 hours of the appearance of the rash.

Active immunization against varicella with live-attenuated VZV was licensed as a single-antigen vaccine in the United States in 1995, and a quadrivalent measles, mumps, rubella, and varicella (MMRV) vaccine was licensed in 2005, both for healthy children age 12 months and older. Varicella vaccines found worldwide are based on the wild Oka strain of VZV, except for the vaccine licensed in South Korea. A single-dose 0.5-mL subcutaneous injection was recommended initially in the United States, which reduced the incidence of disease by 90% by 2008. The universal vaccination effort also resulted in herd immunity, reducing the incidence of disease in unvaccinated individuals. Despite these successes, varicella outbreaks in fully vaccinated children still occurred, in part due to an estimated 9% to 14% vaccine seroconversion failure.

In 2006, the Advisory Committee for Immunization Practices recommended routine varicella vaccination using a 2-dose series, with the first dose at 12 to 15 months and a second dose at 4 to 6 years of age. A 2016 meta-analysis of global varicella effectiveness noted a 10% overall increase in protection with the 2-dose series and a significantly higher seroconversion rate, close to 100%. Another recent 2017 meta-analysis found that the 2-dose varicella vaccine series was more effective in preventing breakthrough varicella in healthy children compared with the single-dose regimen. It was also suggested that the effectiveness of protection against breakthrough varicella was higher when the vaccines were given 3 to 4 years apart. Further studies are needed to evaluate the impact of vaccine spacing, as well as to determine the duration of protection after varicella vaccination.

The varicella vaccine has been found to be safe, with minimal adverse effects. Minor adverse effects, such as pain, swelling, or redness at the injection site, occur in approximately 20% of patients. Rash develops in 1% to 3% of those vaccinated, and 3% may develop a benign varicella-like rash 5 to 26 days after vaccination.

Caution should be used when vaccinating patients with moderate-to-severe illness with or without fever because postvaccine fever can obscure treatment of the concurrent illness. Patients with mild illness, such as upper respiratory tract infection, should be vaccinated. In children with a personal or family history of seizure, MMRV should not be used. Contraindications to varicella vaccination include anaphylaxis to a vaccine component (varicella vaccine contains trace neomycin and hydrolyzed gelatin); congenital or acquired T-lymphocyte immunodeficiency, including leukemia and lymphoma; and children taking long-term immunosuppressant therapy, including high-dose corticosteroid treatment (≥2 mg/kg per day). Children with moderate to severe human immunodeficiency virus (HIV) and those with AIDS should not receive the varicella vaccine. However, children with HIV and CD4 T-lymphocytes of at least 15% may be vaccinated with single-antigen varicella vaccine.

Varicella postexposure management depends on the immune status of the exposed individual and the level of exposure. Significant exposure to varicella includes household contacts, face-to-face contact, or at least 1 hour of exposure in the same room. For healthy, nonimmune patients older than 12 months, varicella vaccine should be administered within 3 days. Prophylaxis with varicella immunoglobulin (VariZIG), or intravenous immunoglobulin if VariZIG is not available, is recommended for populations at risk for severe disease within 96 hours of exposure (and up to 10 days). These high-risk patients include immunocompromised children and pregnant women without evidence of immunity, newborns with maternal varicella exposure within 5 days before and up to 2 days after delivery, preterm infants at least 28 weeks' gestational age born to a nonimmune mother, and infants less than 28 weeks' gestational age or less than 1,000 g at birth regardless of maternal immunity. Patients with bone marrow transplant should receive VariZIG after exposure, regardless of their varicella history. Attention to airborne and contact precautions in hospitalized patients with varicella is critical to prevent spread of infection.

COMMENT: Reviewing this *In Brief* reminded me of the time before vaccine development when varicella was a common illness and most children developed natural immunity from disease. Parents would notify neighbors when their child contracted varicella, and some would have "varicella parties." Parents would bring their children to these parties to purposefully expose their children. Due to the high level of contagion, parents could predict (within 1–2 weeks) the timing of development of the disease. During this period when varicella was so prevalent, both health-care providers and parents were skilled at correctly diagnosing chickenpox in their children by visual inspection, so many questions and cases were handled over the telephone. But since vaccine implementation and a marked decrease in disease, both parents and health-care providers are less familiar with the presentation of varicella and the ability to correctly diagnose it by visual inspection. When in doubt, it makes sense to send a polymerase chain reaction to make a definitive diagnosis (especially for patients who are immunocompromised) both for the benefit of the individual child and for the community and resultant exposure risks.

Another consideration for primary care providers is to remember that because the varicella vaccine is a live attenuated vaccine, children who have received blood products should have administration of this vaccine delayed to develop maximal immunity. The *Red Book* and the Centers for Disease Control and Prevention (CDC) website provide specific information about the time frame for delay, which ranges from 3 to 11 months and is specific to different blood products. The effectiveness of the varicella vaccine is a remarkable example of how immunizations have markedly changed the infectious disease landscape and practice for pediatricians.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

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Leukemia in Children: 1. A; 2. E; 3. B; 4. B; 5. A.

Acute Ataxia in Children: 1. C; 2. A; 3. A; 4. D; 5. C.

Hypoplastic Left Heart Syndrome: An Overview for Primary Care Providers: 1. A; 2. D; 3. E; 4. E; 5. B.

Varicella Zoster Virus

Robyn J. Blair

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Visual Diagnosis

21-day-old Boy with an Umbilical Drainage

Catarina S. Oliveira, MD, MMed,* Inês Pessanha, MD, MMed,†
Liliana Santos, MD, MMed,† Marta Machado, MD, MMed,* Raquel Zenha, MD*

*Department of Pediatrics, Baixo Vouga Medical Center, Aveiro, Portugal
†Department of Pediatric Surgery, Coimbra Hospital and Universitary Centre, Coimbra, Portugal

PRESENTATION

A 21-day-old boy presents to the emergency department for the third time in 24 hours due to a 2-day history of an umbilical mass noted to be draining fluid. The mass is growing in size and increasing its drainage. The patient has an unremarkable medical history, and his umbilical stump fell off when he was 15 days old.

During the patient's first 2 trips to the emergency department, it was assumed that he had a bleeding granuloma. He was first treated with silver nitrate and then with a porcine gelatin absorbable sponge. The physical examination during this third visit reveals a comfortable boy with an umbilical mass that is draining a blood-tinged greenish-yellow liquid. Abdominal palpation seems to cause airflow from a small stoma in the umbilical mass (Fig 1). A catheter is inserted into the stoma, and airflow through the catheter is noted. Additional imaging confirms the diagnosis.

DIAGNOSIS

The physical examination suggests a patent omphalomesenteric duct (POMD). Ultrasonography is performed, revealing a hypoechogenic area between the umbilical mass and the small bowel. No other abdominal anomalies are observed. To better characterize the hypoechogenic mass, fistulography is performed and shows a patent duct between the stoma of the umbilical mass and the small bowel (the contrast injected through the catheter—inserted into the stoma of the umbilical mass—enters the small-bowel lumen) (Fig 2). The patient is taken to surgery, where an OMD covered by small intestine, colic, and gastric epithelium is identified (Fig 3).

DISCUSSION

Differential diagnoses for a draining umbilical mass in neonates include umbilical granuloma (the most common), OMD remnant (POMD or an OMD polyp), patent urachus, and patent umbilical vessel.

The appearance of the mass and the nature of the drainage can guide the diagnosis. A granuloma is a soft, moist, pink, usually pedunculated, friable mass; an OMD remnant is brighter red. (1) The drainage of a urine-like liquid suggests a patent urachus, whereas bilious fluid suggests a POMD. In addition, air discharge

AUTHOR DISCLOSURE Drs Oliveira, Pessanha, Santos, Machado, and Zenha have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

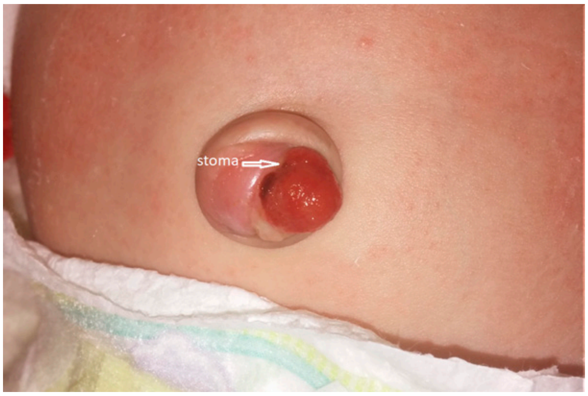

Figure 1. Photograph of the umbilical mass where a small stoma is seen (white arrow).

from an umbilical mass strongly suggests a POMD. A discharge that produces chemical dermatitis may be an ectopic gastric mucosa on an OMD polyp or a POMD. Nevertheless, granuloma tissue is often clinically impossible to distinguish from umbilical remnants. Given such circumstances, clinical suspicion of an umbilical remnant must be placed if the granuloma fails to resolve with silver nitrate after 2 to 3 attempts. (1) Abdominal ultrasonography is generally indicated when there is a suspicion of an umbilical remnant. If physical examination (air or feces are noted to flow through the stoma of the umbilical mass) and ultrasonography support the POMD diagnosis, fistulography may not be necessary. (2)

The OMD or vitelline duct remnant persists in at least 2% of the population, a modest estimate because many cases are asymptomatic and undiagnosed. (3) It is the most common congenital anomaly of the small intestine. (4) The OMD is the primitive connection between the yolk sac, a primordial structure for early embryogenesis, and the embryonic midgut. It provides nourishment and oxygen to the embryo and makes it possible to eliminate metabolic waste. In the fourth week of gestation, the primitive gut forms, and the embryo folds off from the yolk sac. A small part of the yolk sac stays in the embryo, giving rise to the primitive digestive system. The other part lies outside but stays connected to the embryonic digestive tube via a small duct called the OMD or vitelline duct. By the fifth to the ninth weeks of gestation, when fetal organs such as the liver and the placenta begin to perform yolk sac functions, the yolk sac and the OMD involute. (1)(5)

Sometimes, a partial or complete failure of OMD involution occurs. (1) This situation can lead to a spectrum of anomalies in the newborn depending on the stage of arrest of normal involution. When the OMD involutes proximally, there is no connection between the umbilicus and the ileum. In such cases, an umbilical polyp is observed. Such a polyp can manifest itself as an umbilical draining mass, and erosive/irritant dermatitis can appear if the OMD has gastric-like glandular elements. (6)

If the involution occurs distally, persistent tissue at the ileum with no connection to the umbilicus results in Meckel diverticulum, the most common form of OMD remnant. (4) When symptomatic, the most common presentations include lower gastrointestinal bleeding, intussusception and/or bowel obstruction, and features mimicking appendicitis. (3)(7)

The OMD may also persist as a patent mid-duct cyst with closure at both the distal and proximal ends connected to the umbilicus and ileum by a fibrous band or as a fibrous cord between the umbilicus and the ileum. The most common complication of this remnant is bowel obstruction. (3)

Finally, complete patency results in the OMD connecting the umbilicus to the terminal ileum, leading to intestinal drainage from the umbilicus. A "stoma" can be seen in the umbilicus after cord separation. The major reported complications related to POMD include small-bowel obstruction

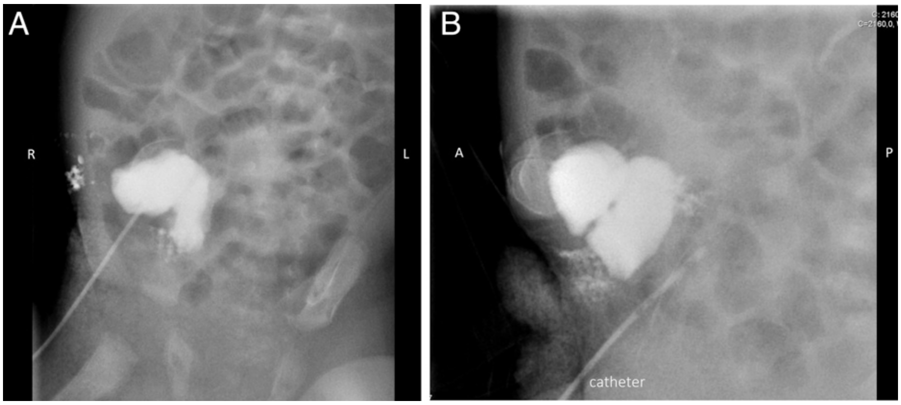

Figure 2. Fistulography (anteroposterior view [A], and lateral view [B]) reveals a patent duct between the umbilical mass and the small bowel as the contrast injected through the catheter (inserted into the stoma of the umbilical mass) entered the small-bowel lumen.

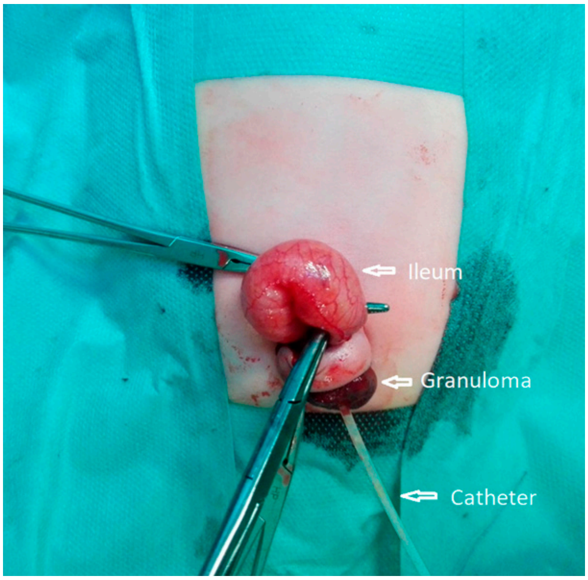

Figure 3. Operative view of the ileum exposed through the surgical incision. The catheter was passed through the umbilical mass into the exposed ileum, confirming the diagnosis of an omphalomesenteric duct.

(if loops of the bowel twist around it), bowel prolapse through the umbilicus, and omphalitis. (7)(8)

Outcomes for infants with POMD improve with earlier diagnosis. Prompt diagnosis allows timely surgical resection of the POMD, thereby preventing complications associated with substantial morbidity and mortality (eg, bowel prolapse through the umbilicus, bowel obstruction, or omphalitis). (3)(7)(8)(9)

The prognosis after complication-free surgery for a POMD is generally excellent; in most cases, no long-term problems occur.

PATIENT COURSE

The patient underwent a laparotomy via a supraumbilical incision, the OMD was isolated, and a wedge resection of the duct was made from the intestinal loop. No other anomalies were identified in the peritoneal cavity. Because of a moderate hemorrhage during the intervention, the patient was given vitamin K. No other complications occurred. The patient was discharged after 5 days and reevaluated 2 weeks later. There was no evidence of complications.

Summary

- Granuloma tissue is the most common cause of a draining umbilical mass. It is a benign lesion, easily treatable with silver nitrate.
- It is often clinically impossible to distinguish an umbilical granuloma from an umbilical remnant.
- If the granuloma fails to resolve with silver nitrate after 2 to 3 attempts, consider an umbilical remnant.
- The appearance of a mass and the nature of the drainage can help the diagnosis.
- Air discharge from a stoma in an umbilical mass strongly suggests a patent omphalomesenteric duct (POMD).
- Abdominal ultrasonography is indicated as the initial study whenever OMD remnants are suspected.
- Early diagnosis of a POMD is important. Timely surgical resection may prevent serious complications.

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Visual Diagnosis: 21-day-old Boy with an Umbilical Drainage

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Visual Diagnosis

Large Mass with Ulceration over the Right Shoulder

Vanessa Amaral, MD,* Joyce Tong, MD,* Kam Ching Chow, MD,*
Jorge Sales Marques, MD*

**Paediatrics Department, Centro Hospitalar Conde São Januário, Macau, China*

PRESENTATION

A 4-month-old girl is referred to pediatric hematology outpatient services with an ulcerated erythematous mass over the right shoulder (Fig 1). A 2-mm macule was noted at 1 week of age, which has gradually increased in size, deepened in color, and protruded from the surface of the skin since 3 weeks of age. This lesion enlarged, developed central ulceration, and began oozing at 3 months of age. The patient is the older of twins born prematurely at 36 weeks and 4 days of gestation via cesarean delivery. Birth weight was 2,600 g. There is no significant medical or family history.

A physical examination reveals a well-appearing infant with an ill-defined, large, erythematous mass measuring 10 × 8 × 5 cm over the right shoulder superimposed with oozing from a central ulceration of 3 × 3.5 × 1 cm. No

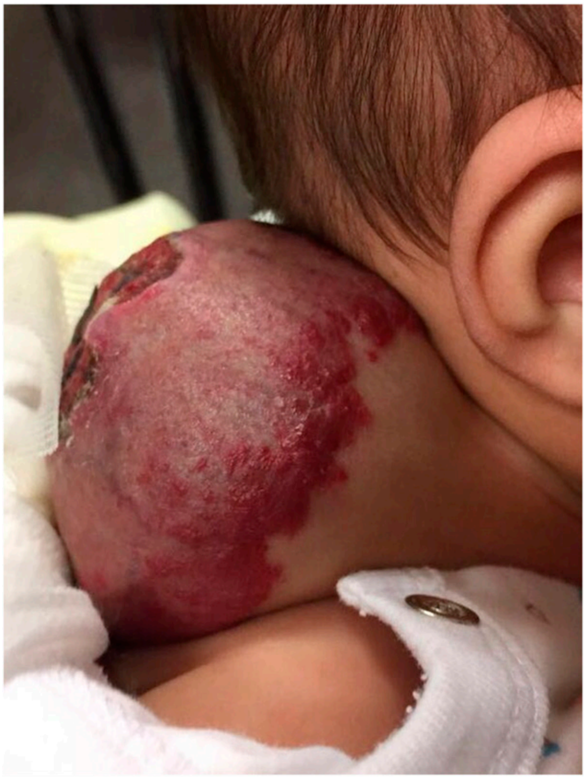

Figure 1. Infantile hemangioma with ulceration over the right shoulder.

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significant pulsation, bruits, or thrills are noted. On palpation the shoulder mass is firm, not movable or compressible. Ultrasonography of the lesion confirms the diagnosis.

DIAGNOSIS

The diagnosis of infantile hemangioma (IH) is made based on clinical presentation, characteristic evolution, and physical examination findings. The diagnosis is subsequently supported by ultrasonography, which reveals a heterogeneous, hyperechogenic, 9 × 8.5 × 5-cm mass with considerable blood flow.

DISCUSSION

IHs are common, benign vascular tumors affecting approximately 4% to 10% of infants and up to 30% of premature babies. IH occurs 4 times more frequently in females than in males. Studies have found that female sex, prematurity, low birth weight, multiple gestation, advanced maternal age, and white race are risk factors for the development of IHs.

The exact pathogenesis of IH has not been elucidated; however, genetic twin studies showed that heredity does not play a major role. Molecular studies showed that upregulation of certain molecular markers, such as glucose transporter protein type-1 (GLUT1) and vascular endothelial growth factor, have been implicated, suggesting that both angiogenesis and vasculogenesis may play an important role in its pathogenesis.

IHs can appear in any part of the body, particularly in the skin, but they most commonly appear in the head and neck region. They may be superficial, appearing as bright red papules or nodules, or they may be deep, appearing as blue or purple lesions. Most lesions follow a characteristic clinical course. They are often not present at birth or may appear as a small dot, with rapid growth during infancy, usually until 6 months of age. An involution phase usually appears after the first few years of life.

Diagnosis of most superficial IHs is often made clinically based on the characteristic clinical course and the classic appearance of a bright colored lesion, which blanches with pressure. Most lesions do not require further investigations; however, deeper lesions may require imaging studies, including ultrasonography or magnetic resonance imaging. Ultrasonography often shows a lesion of increased vessel density and high-flow pattern. Magnetic resonance imaging may demonstrate a well-circumscribed, contrast-enhanced lesion that is isointense on T1-weighted imaging and hyperintense on T2-weighted imaging. Computed tomography and digital subtraction angiography have also been used in a few selected cases; however, risks and benefits should be weighed in view of the radiation exposure to children.

IHs can often be differentiated from other types of benign vascular tumors, such as congenital hemangiomas, in their clinical presentation as well as their histochemical molecular evaluation.

IHs are often not present at birth but develop over the course of weeks, with rapid growth in the first 6 months of life, followed by gradual involution over the next few years. IHs may be associated with other visceral abnormalities as seen in PHACE syndrome. PHACE syndrome is a condition in which IH is associated with ocular, cardiovascular, and brain malformations. The PHACE acronym stands for *p*osterior fossa brain malformation, *h*emangiomas (particularly large and segmental facial lesions), *a*rterial anomalies, *c*ardiac anomalies and coarctation of aorta, and *e*ye abnormalities and endocrine abnormalities. It has a female predominance of 9:1. Hemangiomas in the brain may lead to strokes, seizures, and developmental delay. Lesions close to the ocular region may lead to visual loss, whereas hemangiomas in the ear canal may lead to hearing loss. In view of the potential devastating consequences of this syndrome, a high index of suspicion is necessary to evaluate the possibility of PHACE syndrome in infants with large hemangiomas, particularly on the face or scalp area. Further investigations that should be considered in these infants may include imaging of the head, neck, and chest area, as well as ophthalmologic and audiologic assessments.

Congenital hemangiomas develop during the intrauterine period and, therefore, are present and fully formed at birth. They are typically more reddish-blue or violaceous with telangiectasia and often with a surrounding halo. Depending on their evolution, they can be classified as rapidly involuting congenital hemangioma, which shows rapid involution during the first 18 months of life; noninvoluting congenital hemangioma, which does not show involution and remains unchanged throughout life; and partially involuting congenital hemangioma, which shows partial involution. They have equal sex prevalence. Congenital hemangiomas may be complicated by bleeding and infection. They are not responsive to propranolol therapy (Table).

Immunohistochemical studies showed that only IHs are GLUT-1 stain positive. All other benign vascular tumors are GLUT-1 negative, differentiating them from IHs.

Most IHs resolve spontaneously without any treatment. However, patients with high-risk hemangiomas, including airway hemangiomas, periocular hemangiomas, “beard area” (left and right preauricular area, chin, lower lip, and anterior neck) hemangiomas, facial hemangiomas greater

TABLE. Presentation, Molecular Marker, and Response to Oral Propranolol Treatment in Infantile Hemangioma and Congenital Hemangioma

	INFANTILE HEMANGIOMA	CONGENITAL HEMANGIOMA
Presentation	Usually not present at birth but appears within days or weeks after birth. Approximately half show precursor lesions, eg, red spots, telangiectasia	Present at birth
Sex	Female prevalence (4:1)	Equal sex prevalence
Clinical course	Characteristic rapid growth in first 6 mo after birth, followed by gradual involution over the next few years (5–9 y)	Present and fully formed at birth. Does not progress. Rapid involution (within 12–18 mo) or no involution
Complications	Excess growth, ulceration	Bleeding, infection
Molecular marker	GLUT-1 positive	GLUT-1 negative
Response to oral propranolol treatment	Excellent response	Not effective

GLUT-1=glucose transporter protein type-1.

than 5 cm in diameter or segmental facial hemangiomas, hemangiomas in potentially disfiguring areas particularly in the face, lumbrosacral hemangiomas, and multiple (≥5) hemangiomas, are at risk for severe and permanent sequelae. Complications can occur, including ulceration and massive growth, and could potentially lead to bleeding, pain, irreversible disfiguration, scarring, and an impact on function. Therefore, due to potential cosmetic and functional implications, treatment should be considered when IH is complicated by ulceration or when it is located on the face, particularly in the perioral, ocular, and auricular areas.

Treatment

In the past, medical management of IHs has included topical agents such as corticosteroids, imiquimod, and timolol, as well as systemic therapies, including oral corticosteroids, interferon, and vincristine. Surgery and laser therapy have also been offered to patients; however, these often leave the patient with major adverse effects, including bleeding, infection, and scar formation.

In 2008, a novel therapy with a nonselective β-blocker, propranolol, was found incidentally to be effective in the treatment of IH. Propranolol is believed to cause regression of the lesion via 3 different mechanisms: vasoconstriction in the early phase, inhibition of angiogenesis in the intermediate phase, and induction of apoptosis in the delayed phase.

Common dosages of oral propranolol range from 1 to 3 mg/kg per day. Often an initial dose of 1 to 2 mg/kg per day is used and is titrated to 3 mg/kg per day over several days according to clinical response.

Common adverse effects of propranolol use include somnolence, cold extremities, diarrhea, and fatigue. Serious adverse effects that have been reported are hypoglycemia, bradycardia, hypotension, bronchospasm, and worsening of congestive heart

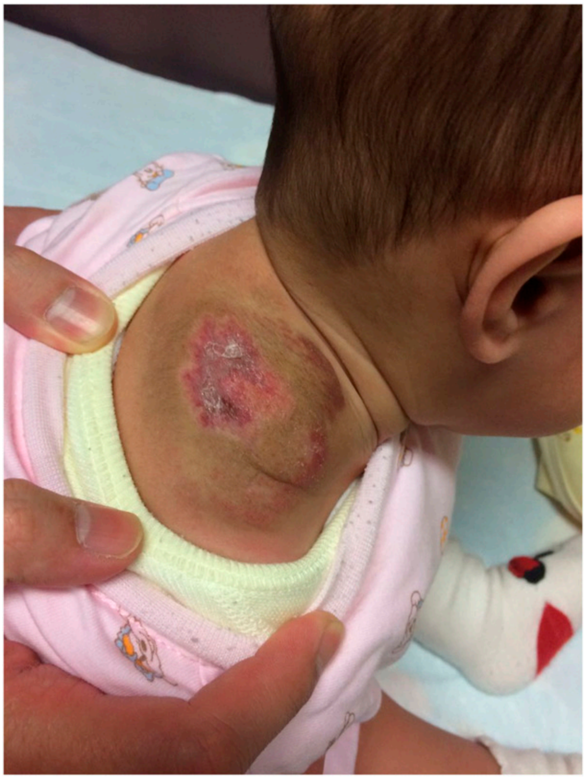

Figure 2. Infantile hemangioma after 2 months of oral propranolol treatment. There is substantial reduction of the lesion site and complete healing of the central ulceration.

failure. Propranolol may increase the risk of stroke in patients with PHACE syndrome. Therefore, propranolol is contraindicated in patients with asthma, heart block or bradycardia, heart failure, or pheochromocytoma. Propranolol should also be avoided in preterm patients with a postmenstrual age younger than 45 weeks or body weight less than 4.5 lb (<2 kg). It has been shown that efficacy is best when treatment is started within 6 months of age; therefore, early diagnosis and prompt treatment may lead to best treatment results.

Patient Course

The patient was started on oral propranolol 2 mg/kg per day in 2 divided doses at 5 months of age. The ulceration stopped oozing, and the lesion had a noticeable reduction in erythema and size within 1 week of starting oral propranolol therapy. The patient tolerated the treatment well without any adverse effects. There was continued improvement after 2 months of treatment, with further reduction in lesion size and complete healing of ulceration (Fig 2).

Summary

- Infantile hemangiomas (IHs) are the most common benign vascular tumors of infancy.
- Most IHs go through a rapid course of proliferation followed by a gradual involution without treatment. Some cases are complicated with bleeding, ulceration, functional impairment, and severe disfigurement. These lesions may benefit from treatment.
- There is increasing evidence supporting the use of oral propranolol in the treatment of IHs. Best results are seen when treatment is started before 6 months of age. Timely recognition, prompt diagnosis, and treatment may minimize the growth and prevent the development of scarring and other complications.

Suggested Readings

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Tickborne Diseases in Children in the United States

Jennifer S. Read, MD, MS, MPH, DTM&H*[†]

*Department of Pediatrics, University of Vermont Medical Center, Burlington, VT

[†]Infectious Disease Epidemiology, Vermont Department of Health, Burlington, VT

Practice Gaps

The most common tick-borne infections in the United States are Lyme disease, ehrlichiosis, anaplasmosis, Rocky Mountain spotted fever, and babesiosis. The epidemiology of these infections in the United States is integrally related to the geographic distribution and seasonality of the tick vector of each of the infections. Because these infections can be very serious and sometimes fatal, and because of the inherent delay in obtaining laboratory confirmation (especially with serologic assays requiring acute and convalescent titers), considering early implementation of empirical treatment based on the patient's clinical presentation is extremely important. Prevention of acquisition of tick-borne diseases requires avoiding tick-infested areas or, if this is not possible or desired, implementing steps to decrease the likelihood of tick bites and the duration of tick attachment.

Objectives

After completing this article, readers should be able to:

1. Understand the etiologic organisms and the associated ticks responsible for transmission, the geographic distribution of and the reported infections associated with the ticks in the United States, and the seasonality and incubation periods of tick-borne infections in the United States.
2. Recognize the clinical manifestations and laboratory abnormalities associated with the infections, especially as they relate to children.
3. Plan for the diagnosis, treatment, and prevention of these infections.

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ABBREVIATIONS

CSF	cerebrospinal fluid
EM	erythema chronicum migrans
IFA	immunofluorescent antibody
Ig	immunoglobulin
RMSF	Rocky Mountain spotted fever
PCR	polymerase chain reaction

INTRODUCTION

Vector-borne diseases, caused by microorganisms transmitted by insects and ticks, are major causes of morbidity and mortality globally. In the United States, vector-borne diseases are occurring more frequently and represent a significant public health concern. (1) The numbers of reported vector-borne disease cases in the United States (tick-borne, mosquito-borne, and flea-borne diseases) are shown in Table 1. (1) The reported incidence of vector-borne diseases most likely significantly underestimates the actual occurrence of these diseases; some individuals with vector-borne infections may be asymptomatic or, if symptomatic, may not seek medical care.

This review addresses the most common tick-borne diseases reported in the United States, (1) specifically, Lyme disease, ehrlichiosis and anaplasmosis, spotted fever rickettsiosis, including Rocky Mountain spotted fever (RMSF), and babesiosis. Specifically, the following are discussed: the organisms and the associated ticks responsible for transmission; the geographic distribution of and the reported infections associated with the ticks in the United States; the seasonality of tick-borne infections in the United States; the infections' incubation periods; the clinical manifestations and laboratory abnormalities associated with the infections, especially as they relate to children; and the diagnosis, treatment, and prevention of these infections.

LYME DISEASE

Lyme disease is the most common tick-borne infection in the United States. (2) Over a 12-year period ending in 2016, 402,502 cases of Lyme disease were reported in the United States. (1) Table 2 summarizes characteristics of *Borrelia burgdorferi* sensu stricto (*B burgdorferi*), the causative organism of Lyme disease in the United States. The first report in the United States of the skin lesion characteristic of Lyme disease, erythema chronicum migrans (EM), was published in 1970. (3) Subsequently, the full spectrum of clinical manifestations of Lyme disease, including EM, was described in 1977. (4) *B burgdorferi*, a spirochete in the family Spirochaetaceae, (5) was first isolated in 1982. (6) Another *Borrelia* species (*Borrelia miyamotoi*) was first identified in Japan in the 1990s, (7) and subsequently the first case in the United States was described. (8)

B burgdorferi infection is transmitted by the blacklegged tick (*Ixodes scapularis*) (Fig 1) and the western blacklegged tick (*Ixodes pacificus*). (2) *B miyamotoi* is transmitted by the same tick vectors as *B burgdorferi*. (9)(10)(11)(12) The seasonality of Lyme disease is summarized in Table 2. (5) In the United States, most cases of Lyme disease are reported from 2 regions: 1) New England through the mid-Atlantic states and 2) the upper Midwest states (Table 2, Fig 2). (5)(13) *B miyamotoi* infections have similar seasonality and distribution as Lyme disease cases. (9)(10)(12)

TABLE 1. **Vector-borne Disease Cases Reported to the National Notifiable Disease Surveillance System—US States and Territories, 2004–2016**

DISEASE	NO. CASES
Tick-borne diseases	
Lyme disease	402,502
Anaplasmosis/ ehrlichiosis	39,959
Spotted fever rickettsiosis	37,376
Babesiosis	9,631
Tularemia	2,102
Powassan virus	101
Subtotal	491,671
Mosquito-borne diseases	
Dengue viruses	46,692
Zika virus	41,680
West Nile virus	31,919
Malaria	20,167
Chikungunya virus	9,081
California serogroup viruses	1,063
St Louis encephalitis virus	133
Eastern equine encephalitis virus	106
Yellow fever virus	1
Subtotal	150,842
Flea-borne disease (plague)	89
Total	642,602

Adapted from Rosenberg R, Lindsey NP, Fischer M, et al. Vital signs: trends in reported vectorborne disease cases—United States and Territories, 2004-2016. MMWR Morb Mortal Wkly Rep. 2018;67(17):496–501.

The incubation period and clinical manifestations of, and the laboratory abnormalities associated with, Lyme disease are summarized in Table 3. (2)(5)(13) The clinical manifestations of Lyme disease occur in 3 stages: early localized, early disseminated, and late. (5) Early localized disease (2)(5)(13) is characterized by EM at the site of the tick bite and systemic manifestations. In children, EM is the most common manifestation of Lyme disease. Some patients with large EM lesions are misdiagnosed as having cellulitis. Only a minority of patients have the classic bull's-eye appearance (concentric rings). Several weeks after the tick bite, the next stage of Lyme disease (early disseminated disease) (2)(5),(13)

TABLE 2. **Tick-borne Diseases in Children in the United States: Organisms, Vectors, Seasonality, and Geographic Distribution**

DISEASE	ORGANISM	VECTOR	SEASONALITY	GEOGRAPHIC DISTRIBUTION
Lyme disease	*Borrelia burgdorferi* sensu stricto *(B burgdorferi)*	Blacklegged tick *(Ixodes scapularis)* and the western blacklegged tick (*Ixodes pacificus*)	Most early localized, early disseminated disease: April–October >50% during June and July	>90% of cases reported from New England (Maine, New Hampshire, Vermont, Connecticut, Rhode Island, Massachusetts) and the northeastern and mid-Atlantic states (Delaware, Maryland, New Jersey, New York, Pennsylvania, Virginia) Less frequently, Lyme disease is reported from the upper Midwest (especially Minnesota and Wisconsin) Some cases have been reported from northern California, Oregon, and Washington
Ehrlichiosis	*Ehrlichia chaffeensis*	Lone star tick (*Amblyomma americanum*)	Most infections: April–September Peak incidence: May–July	Predominantly southeast, south central, east coast states Highest incidence in Arkansas, Delaware, Missouri, Oklahoma, Tennessee, Virginia
	Ehrlichia ewingii	Lone star tick (*A americanum*)	Most infections: April–September Peak incidence: May–July	Mostly southeastern, south central, midwestern states
	Ehrlichia muris–like organism	Possibly blacklegged tick (*I scapularis*)	Highest incidence: April–September Can occur year-round in areas with endemic disease	Minnesota, Wisconsin
Anaplasmosis	*Anaplasma phagocytophilum*	Blacklegged tick *(I scapularis)* or western blacklegged tick *(I pacificus)*	Most infections: June–November	Most frequently reported from northeastern and upper midwestern states
RMSF	*Rickettsia rickettsii*	American dog tick (eastern, central, western United States) Rocky Mountain wood tick in Rocky Mountain states Brown dog tick in southwestern United States and along US-Mexico border	Highest incidence: April–September (but, in areas with endemic disease, can occur year-round)	Throughout most of the continental United States In 2002–2012, 5 states accounted for 63% of cases (Arkansas, Missouri, North Carolina, Oklahoma, Tennessee) Has become more common in parts of Arizona
Babesiosis	*Babesia microti* and other *Babesia* species	Blacklegged tick *(I scapularis)*	Most infections during late spring, summer, or fall	Northeast (especially Connecticut, Massachusetts, New Jersey, New York, Rhode Island; also, Maine, Pennsylvania) Upper Midwest (Minnesota and Wisconsin)

may manifest as multiple EM lesions. Other clinical manifestations may occur (with or without multiple EM lesions), including neurologic, cardiac, and systemic manifestations. Late Lyme disease (2)(5)(13) occurs in individuals who were not treated during the early localized or early disseminated stages of infection. Several months may pass between a tick bite and late Lyme disease manifestations. Children with late Lyme disease usually present with arthritis. Because some patients with Lyme disease do not report a history of clinical features of early localized or early disseminated

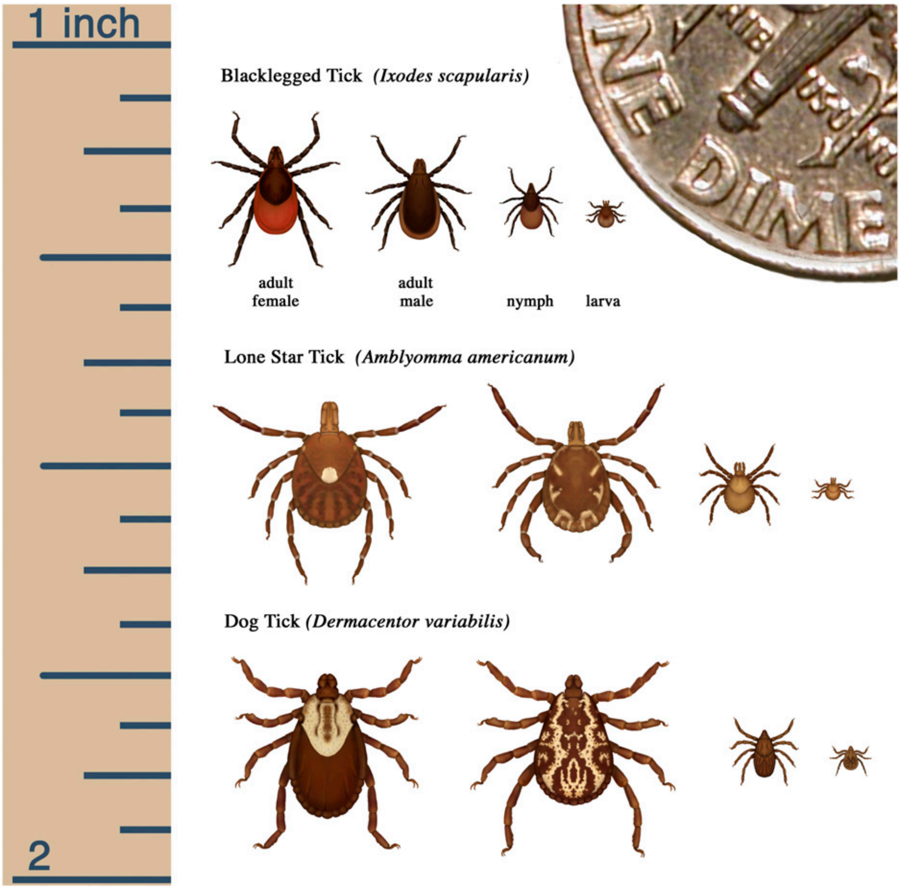
1 inch
2
Blacklegged Tick (Ixodes scapularis)
adult female
adult male
nymph
larva
Lone Star Tick (Amblyomma americanum)
Dog Tick (Dermacentor variabilis)
ONE DIME

Figure 1. Ticks that commonly bite humans. (Reprinted with permission from Centers for Disease Control and Prevention. *Tickborne Diseases of the United States*. 5th ed. Atlanta, GA: Centers for Disease Control and Prevention; 2018.)

Lyme disease, arthritis and other manifestations of late Lyme disease may occur in patients without a history of EM. Patients with *B miyamotoi* infections most commonly report systemic manifestations (fatigue, headache, arthralgia, myalgia, nausea) as well as high fever (temperature >104°F [>40°C]), which may be recurrent, and chills. (14)(15)(16)(17)(18) Laboratory abnormalities observed in patients with Lyme disease (13) include an elevated erythrocyte sedimentation rate, elevated hepatic transaminase concentrations, and microscopic hematuria or proteinuria. With Lyme meningitis, the cerebrospinal fluid (CSF) usually has a lymphocytic pleocytosis, a slightly elevated protein concentration, and a normal glucose concentration. Leukopenia, thrombocytopenia, and elevated liver enzyme concentrations have been reported with *B miyamotoi* infection. (19)

Diagnostic assays for Lyme disease are summarized in Table 4. (2)(5)(13) Of note, the diagnosis of Lyme disease depends heavily on a compatible clinical presentation along with plausible geographic exposure to the tick vector. Patients with early Lyme disease with EM may be treated presumptively (and serologic testing is not recommended). (5) The laboratory diagnosis of Lyme disease involves demonstration of *B burgdorferi* antibodies in serum. A 2-step laboratory testing protocol is recommended. First, an enzyme-linked immunosorbent assay or an immunofluorescent antibody (IFA) assay is performed. If the result of the antibody assay is positive or equivocal, the second-tier standardized Western immunoblot is necessary. If Lyme meningitis is suspected, the CSF can be tested for immunoglobulin (Ig) M or IgG antibodies. There are several important considerations for serologic testing for Lyme disease. (13) First, antibody titers are often negative if the serum specimen was obtained during the first few weeks of infection. Second, in those with more than 1 month of illness, only IgG testing should be performed (not IgM testing). Third, because of antibody persistence, a single positive serologic assay result cannot reliably distinguish between previous and current infection. Fourth, serologic assays cannot be used to assess response to treatment. Fifth,

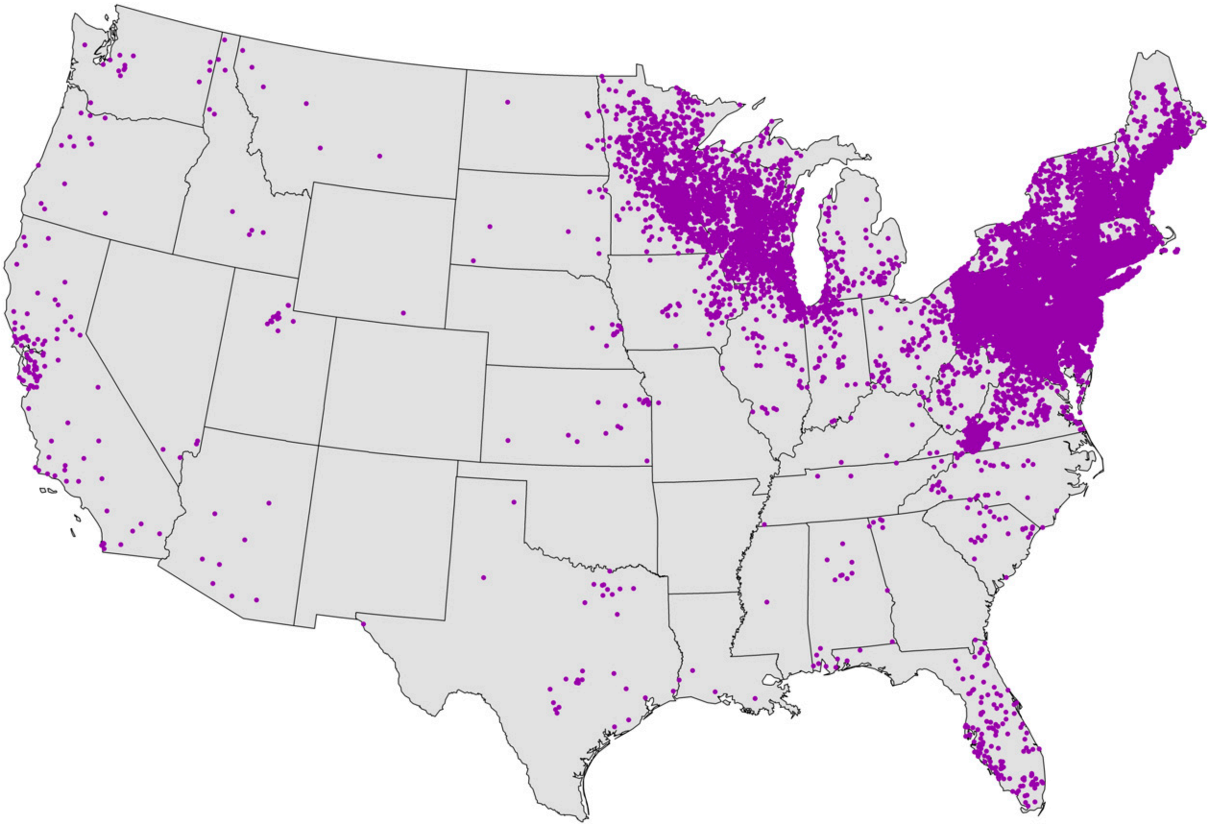

Figure 2. Lyme disease cases reported to the Centers for Disease Control and Prevention, 2016. (Reprinted with permission from Centers for Disease Control and Prevention. *Tickborne Diseases of the United States.* 5th ed. Atlanta, GA: Centers for Disease Control and Prevention; 2018.)

and most importantly, serologic assays may yield false-positive results; there may be cross-reactivity with antibodies to other spirochetes and to certain viruses (including Epstein-Barr virus and varicella) and there may be false-positive results in patients with certain autoimmune diseases (eg, systemic lupus erythematosus). It is, therefore, important to perform Lyme disease testing with an appropriate epidemiologic history of potential contact with tick vectors associated with transmitting Lyme disease and compatible clinical manifestations. The laboratory diagnosis of *B miyamotoi* infection can be accomplished by identification of the spirochetes on blood smears or CSF samples (if neurologic manifestations), through polymerase chain reaction (PCR) assays performed on blood or CSF samples, and with serologic assays. (19)

Treatment of Lyme disease is summarized in Table 4. (5)(13) Antibiotic therapy for patients who are asymptomatic (but seropositive) or who have nonspecific symptoms is not recommended. As noted previously herein, patients with EM can be treated presumptively. *B miyamotoi* infections can be treated with doxycycline or amoxicillin. (20)

EHRLICHIOSIS AND ANAPLASMOSIS

Between 2004 and 2016, 39,959 cases of ehrlichiosis and anaplasmosis were reported in the United States (1) Table 2 summarizes characteristics of the causative organisms. Ehrlichiosis and anaplasmosis are caused by infections with Gram-negative cocci of the family Anaplasmataceae, which are obligate intracellular bacteria. (21)(22)(23)(24) In the United States, ehrlichiosis is caused by 1 of 3 different species of *Ehrlichia* (*Ehrlichia chaffeensis*, *Ehrlichia ewingii*, and *Ehrlichia muris eauclairensis*). *E chaffeensis,* first described in 1987, is the most common cause of human ehrlichiosis in the United States. (25) The other species of *Ehrlichia* were recognized in the 1990s. (26)(27) Anaplasmosis in the United States is caused by *Anaplasma phagocytophilum* and was first described in humans in the 1990s. (28) These organisms have a tropism for leukocytes (*Ehrlichia* species: usually monocytes or tissue macrophages; *A phagocytophilum*: usually granulocytes). (21)(22)(23)(24)

Both *Ehrlichia* species and *A phagocytophilum* are transmitted by ticks, but *A phagocytophilum* also can be transmitted

TABLE 3. Tick-borne Diseases in Children in the United States: Incubation Period, Clinical Manifestations, and Laboratory Abnormalities

DISEASE	INCUBATION PERIOD	CLINICAL MANIFESTATIONS	LABORATORY ABNORMALITIES
Lyme disease	3–32 d (median, 11 d)	Early localized stage: • EM rash: o Begins with a red macule or papule, which subsequently (over a period of days to weeks) expands to form a large, erythematous, annular lesion, with or without central clearing o Usually painless (but not always) and usually nonpruritic o Variable in terms of size and shape (size usually ≥5 cm) o May have a central vesicular component, purplish discoloration, or necrosis • Systemic manifestations: fever (usually mild), malaise, headache, myalgia, arthralgia Early disseminated stage: • Multiple EM lesions (similar to but smaller than primary lesion) • Other manifestations (with or without EM lesions): o Cranial nerve palsies (usually cranial nerve VII) o Lymphocytic meningitis (often with papilledema or cranial neuropathy) o Radiculitis o Carditis (atrioventricular block of varying degree) (occurs less commonly in children) o Systemic manifestations: fever (usually mild), fatigue, headache, myalgia, arthralgia Late disseminated stage: • Arthritis (usually monoarticular or pauciarticular; affecting large joints [especially knees]) • Other rare manifestations: o Pseudotumor cerebri o Encephalitis o Encephalopathy o Polyneuropathy	• Elevated erythrocyte sedimentation rate • Mildly elevated hepatic transaminase concentrations • Microscopic hematuria or proteinuria • If Lyme meningitis: CSF typically shows lymphocytic pleocytosis, slightly elevated protein, and normal glucose
Ehrlichiosis	5–14 d	• Systemic manifestations: fever, chills, malaise, headache, myalgia, nausea • Gastrointestinal manifestations (abdominal pain, vomiting, diarrhea) (more common in children) • Rash (petechial, maculopapular, or diffuse erythema, usually affecting the trunk and extremities) (more common in children) • Severe manifestations: toxic shock– or septic shock–like syndromes, renal failure, hepatic failure, coagulopathies, hemophagocytic lymphohistiocytosis	• Leukopenia and thrombocytopenia • Anemia – occurs later than leukopenia or thrombocytopenia • Hyponatremia • Elevated serum hepatic transaminase concentrations • CSF abnormalities (pleocytosis with predominance of lymphocytes, increased total protein concentration) • Morulae may be visualized during acute illness
Anaplasmosis	5–14 d	• Systemic manifestations: see ehrlichiosis • Gastrointestinal and CNS manifestations less frequent than in ehrlichiosis • Rash in <10% • Severe manifestations (see ehrlichiosis), less common than in ehrlichiosis	• Leukopenia and thrombocytopenia • Hyponatremia • Elevated serum hepatic transaminase concentrations • Morulae may be visualized during acute illness

Continued

TABLE 3. **(Continued)**

DISEASE	INCUBATION PERIOD	CLINICAL MANIFESTATIONS	LABORATORY ABNORMALITIES
RMSF	3–12 d	Early (1–4 d): • Fever, chills, malaise • Severe headache (less common in young children) • Myalgia • Gastrointestinal symptoms (abdominal pain, nausea, vomiting, anorexia) • Edema, periorbital or on the back of hands • Photophobia Late (5+ d): • Altered mental status, coma • Respiratory compromise (pulmonary edema, ARDS) • Necrosis (may require amputation) • Multiorgan system damage (eg, CNS, renal) Rash: • Early (2–5 d after onset of symptoms): maculopapular rash on wrists and ankles, often spreading within hours, both proximally to the trunk and distally to the palms and soles (face is usually spared) • Late (day 6 or later after onset of symptoms): petechial rash	• Thrombocytopenia • Hyponatremia • Elevated liver transaminase concentrations • Leukopenia • Anemia
Babesiosis	1–9 wk	• Often asymptomatic or associated with only mild, nonspecific symptoms but can be a severe, potentially fatal disease • Fever common • Gradual onset of symptoms such as fatigue, malaise, and anorexia • Subsequently, influenzalike illness symptoms (fever, chills, arthralgia, myalgia, headache, nausea) • Other, less common symptoms: conjunctival injection, photophobia, pharyngitis, nonproductive cough, abdominal pain, vomiting, weight loss, emotional lability • Possible respiratory distress, hypotension, mild hepatosplenomegaly, jaundice, dark urine, depression • Disseminated intravascular coagulation, renal failure, hemodynamic instability, respiratory distress, hepatic compromise, altered mental status, and death may occur with severe infection	• Hemolytic anemia. elevated reticulocyte count • Thrombocytopenia • Proteinuria • Elevated concentrations of hepatic enzymes, creatinine, and blood urea nitrogen

ARDS=acute respiratory distress syndrome, CNS=central nervous system, CSF=cerebrospinal fluid, EM=erythema chronicum migrans.

through blood product transfusion. (21)(22)(23)(24) Tick vectors in the United States for these organisms (Table 2) include the lone star tick (*Amblyomma americanum*) (Fig 1), the blacklegged tick (*I scapularis*) (Fig 1), and the western blacklegged tick (*I pacificus*). (21)(22)(23)(24) The seasonality (21)(22)(23)(24) and geographic location (21)(22)(23)(24)(29) of infections with *Ehrlichia* species and *A phagocytophilum* are summarized in Table 2. In the United States, ehrlichiosis is most often reported from southeastern and south-central states (from the east coast to Texas) (Table 2, Fig 3), whereas anaplasmosis is most often reported from the northeastern and upper midwestern states (Table 2, Fig 4).

The incubation periods (21)(22)(23)(24) and clinical manifestations (30)(31)(32)(32) of, and the laboratory abnormalities (30)(33)(34) associated with, ehrlichiosis and anaplasmosis are summarized in Table 3. Many of the clinical manifestations of ehrlichiosis and anaplasmosis likely result from the body's systemic inflammatory response and not from direct effects of the bacteria. (24) The estimated case fatality rates among those with ehrlichiosis and anaplasmosis seeking medical care are 3% and less than 1%, respectively. (33)(35)(36)(37)(38) Although the incidence of ehrlichiosis due to *E chaffeensis* generally increases with increasing age, (29)(36)(39) the case fatality

TABLE 4. Tick-borne Diseases in Children in the United States: Diagnosis and Treatment

DISEASE	DIAGNOSIS	TREATMENT
Lyme disease	• Demonstration of diagnostic IgM or IgG antibodies in serum. A 2-tiered testing protocol is recommended: enzyme-linked immunosorbent assay or IFA assay should be performed first; if positive or equivocal, Western blot should follow • In suspected Lyme meningitis, testing for intrathecal IgM or IgG antibodies	Early localized disease: • Doxycycline 4.4 mg/kg per day, PO, divided BID (maximum, 200 mg/d) for 10 ds; OR • Amoxicillin 50 mg/kg per day, PO, divided TID (maximum, 1,500 mg/d) for 14 d; OR • Cefuroxime 50 mg/kg per day, PO, divided BID (maximum, 100 mg/d) for 14 d For patients intolerant to the above: • Azithromycin 10 mg/kg per day, PO, once daily for 7 d Extracutaneous disease: • Isolated facial palsy: doxycycline 4.4 mg/kg per day, PO, divided BID (maximum, 200 mg/d) for 14 d • Arthritis: an oral drug as for early localized disease, for 28 d • Persistent arthritis after first course of therapy: treat again using an oral agent as for first-episode arthritis for 28 d; OR ceftriaxone 50–75 mg/kg, IV, once daily (maximum, 2,000 mg/d) for 14–28 d • Atrioventricular heart block or carditis: an oral agent as for early localized disease, for 14 d (range, 14–21 d); OR ceftriaxone 50–75 mg/kg, IV, once daily (maximum, 2,000 mg/d) for 14 d (range, 14–21 d if hospitalized; can be changed to oral therapy once stabilized/discharged) • Meningitis: doxycycline 4.4 mg/kg per day, PO, divided into doses (maximum, 200 mg/d) for 14 d; OR ceftriaxone 50–75 mg/kg, IV, once daily (maximum, 2,000 mg/d) for 14 d
Ehrlichiosis	• PCR assay to detect Ehrlichia DNA in whole blood • IFA assay: demonstration of a 4-fold rise in the Ehrlichia IgG-specific antibody titer in a pair of serum samples[a] • Immunohistochemical staining of skin, tissue, or bone marrow specimens to visualize Ehrlichia species	Doxycycline (maximum, 100 mg per dose): • Children weighing <100 lb (<45.4 kg): 2.2 mg/kg per dose BID, PO or IV • Larger children and adults: 100 mg BID, PO or IV Duration of therapy: minimum, 5–7 days; therapy should be given until evidence of clinical improvement and at least 3 d after fever resolves
Anaplasmosis	• PCR assay to detect Anaplasma phagocytophilum DNA in blood[b] • IFA assay: demonstration of a 4-fold rise in the A phagocytophilum IgG-specific antibody titer in a pair of serum samples[a] • Immunohistochemical staining of skin, tissue, or bone marrow specimens to visualize A phagocytophilum	Doxycycline (maximum, 100 mg per dose): • Children weighing less than 100 lb (45.4 kg): 2.2 mg/kg per dose BID, PO or IV • Larger children and adults: 100 mg BID, PO or IV Duration of therapy: 10–14 d
RMSF	• IFA assay: demonstration of a 4-fold change (usually an increase) in IgG-specific antibody titers in paired serum samples (first sample obtained within first week of illness; second obtained 2–4 wk later)[a] • PCR assay for detection of rickettsial DNA in a biopsy specimen (eg, skin biopsy of a rash lesion) • Immunohistochemical staining of rickettsial organisms from biopsy specimen (eg, skin or other tissue)	Doxycycline (maximum, 100 mg per dose): • Children weighing <100 lb (<45.4 kg): 2.2 mg/kg per dose BID, PO or IV • Larger children and adults: 100 mg BID, PO or IV Duration of therapy: minimum, 5–7 d; therapy should be given until evidence of clinical improvement and at least 3 d after fever resolves

Continued

TABLE 4. **(Continued)**

DISEASE	DIAGNOSIS	TREATMENT
Babesiosis	• Microscopic examination of Giemsa- or Wright-stained peripheral blood smears to identify intra-erythrocytic Babesia parasites[c] • PCR assay for detection of Babesia species DNA in blood[d] • IFA assay to detect Babesia-specific antibodies in blood[e]	Dosages for children: • Atovaquone 20 mg/kg every 12 h (maximum, 750 mg per dose); AND azithromycin 10 mg/kg (maximum, 500 mg per dose) on day 1 and 5 mg/kg every day (maximum, 250 mg per dose) subsequently • Clindamycin 7–10 mg/kg, IV or PO, every 6–8 h (maximum, 600 mg per dose); AND quinine 8 mg/kg PO every 8 h (maximum, 650 mg per dose) Duration of therapy: 7–10 d

BID=twice daily; IFA=immunofluorescent antibody, Ig=immunoglobulin, IV=intravenous, PCR=polymerase chain reaction, PO=orally, TID=three times daily.

[a] *Antibody titers are often negative if the serum specimen was obtained during the first 7 to 10 days of illness. Antibody results obtained in the first (acute) sample cannot be relied on alone for laboratory confirmation of the diagnosis. Because IgM antibodies are less specific than IgG antibodies (and more likely to generate false-positive results), IgM results should not be used alone for laboratory diagnosis.*

[b] *PCR assays are most sensitive during the first week of illness, but the sensitivity may decrease after the administration of drugs in the tetracycline class.*

[c] *Multiple smears may need to be examined, and if the diagnosis of babesiosis is being considered, the laboratory should be notified that a manual (not an automated) review of blood smears for Babesia parasites is needed. It may be difficult to distinguish between Babesia organisms and Plasmodium falciparum or artifacts; examination of blood smears by a reference laboratory should be considered.*

[d] *In patients with low-grade B microti parasitemia (eg, early in the infection when parasites are more difficult to visualize on blood smear), PCR assays seem to have higher sensitivity than blood smear microscopy. Of note, PCR assays should be used with caution when monitoring a patient's response to therapy because B microti organisms can be detected for a long period (weeks to months) after the parasites can no longer be visualized on microscopic examination of blood smears.*

[e] *This method is particularly useful for diagnosing babesiosis in individuals with very low levels of parasitemia and those in whom discrimination between babesiosis and malaria is difficult because of inconclusive blood smear examination and/or a travel history that cannot exclude either parasite.*

rates are highest in both adults 70 years or older and children 10 years or younger. (29)(36) Ehrlichiosis in immunocompromised individuals is associated with an increased risk of death, (29)(36) but severe or fatal cases of ehrlichiosis have occurred in previously healthy children and young adults. (33)(40) Children with ehrlichiosis often are asymptomatic or only mildly symptomatic. (33)(35)(41) With ehrlichiosis, gastrointestinal manifestations and rash may be more common in children. (33)(41) More severe manifestations of ehrlichiosis include toxic shock– or septic shock–like syndromes, coagulopathies, renal failure, and hepatic failure. (42) Rarely, *E chaffeensis* infection may result in hemophagocytic lymphohistiocytosis. (41)(43) Anaplasmosis is usually a self-limiting illness. (24) Gastrointestinal manifestations and central nervous system involvement occur less frequently in patients with anaplasmosis than in those with ehrlichiosis, (30)(44) and rash occurs in less than 10% of patients with anaplasmosis. (30)(44) Severe or life-threatening manifestations are less frequent with anaplasmosis than with ehrlichiosis. Factors associated with a more severe clinical course of ehrlichiosis or anaplasmosis include immunosuppression and delay in diagnosis or treatment. In cases of anaplasmosis, laboratory abnormalities are usually observed during the first week of clinical illness, and usually there are no CSF abnormalities. (38) The organisms (*Ehrlichia* species and *A phagocytophilum*) multiply within cytoplasmic vacuoles of the target cells (monocytes or granulocytes), forming clusters of bacteria called *morulae*. (45) Such morulae may be visualized in the cytoplasm of these cells during the acute stage of illness and are highly suggestive of the diagnosis (but because examination of a blood smear is insensitive, finding morulae should not be used alone to rule in or rule out the diagnosis). Patients with anaplasmosis may have altered neutrophil function, which could result in neutrophils having ineffective microbicidal activity. (40)

Diagnostic assays for ehrlichiosis and anaplasmosis are summarized in Table 4. For both diseases, laboratory diagnosis can be accomplished in 3 different ways (21)(22)(23)(24): PCR assays to detect the organism's DNA, IFA assays to detect antibodies against the organism, and immunohistochemical staining to visualize the organisms in tissue specimens.

Treatment of ehrlichiosis and anaplasmosis is summarized in Table 4 (21)(22)(23)(24). The first-line treatment for either disease is doxycycline. A clinical suspicion of ehrlichiosis or anaplasmosis is sufficient to initiate treatment.

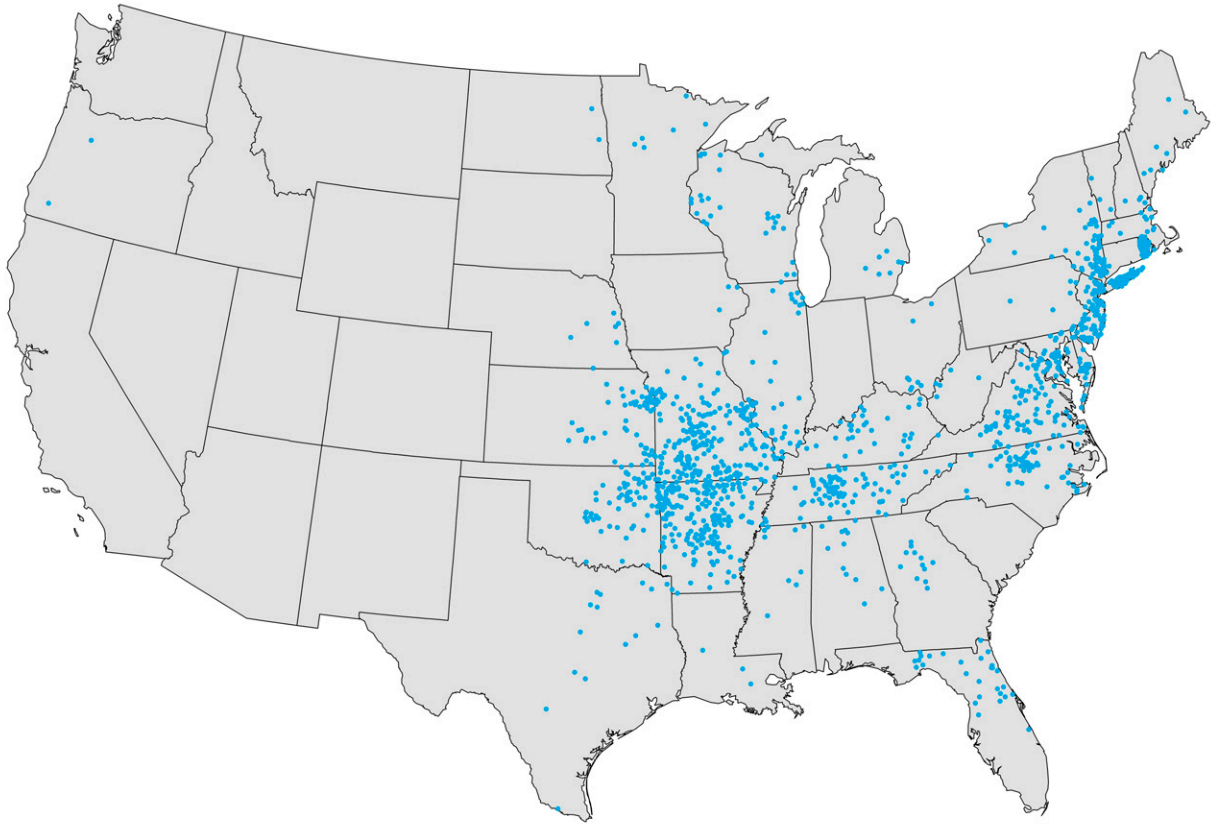

Figure 3. Ehrlichiosis cases reported to the Centers for Disease Control and Prevention, 2016. (Reprinted with permission from Centers for Disease Control and Prevention. *Tickborne Diseases of the United States.* 5th ed. Atlanta, GA: Centers for Disease Control and Prevention; 2018.)

Conversely, delaying initiation of treatment may result in severe illness or death.

ROCKY MOUNTAIN SPOTTED FEVER

A total of 37,376 infections with spotted fever group rickettsii (including *Rickettsia rickettsii*, *Rickettsia parkeri,* and *Rickettsia* species 364D) were reported in the United States from 2004 through 2016. (1) Table 2 summarizes characteristics of *R rickettsii*, the causative organism of RMSF, first described in 1906. (46) *R rickettsii*, a member of the family Rickettsiaceae, is an obligate intracellular, Gram-negative bacillus. (24)(47)(48) The organism primarily targets endothelial cells of the vascular system, inducing a diffuse vasculitis with resultant increased vascular permeability. (24)

The tick vector, (24)(47)(48) seasonality, (24)(47)(48) and geographic distribution of reported cases (49)(50)(51)(52)(53) are summarized in Table 2. *R rickettsii* is transmitted by 3 different ticks (24)(47)(48): the American dog tick (*Dermacentor variabilis*) (Fig 1), the Rocky Mountain wood tick (*Dermacentor andersoni*), and the brown dog tick (*Rhipicephalus sanguineus*). RMSF and related rickettsioses have been reported throughout most of the continental United States but are more common in certain south/south central states (Table 2, Fig 5). (49)(50)(51)(52)(53)

The incubation period (54) and clinical manifestations (24)(47)(48)(55)(56)(57)(58)(59) of, and laboratory abnormalities associated with, RMSF are summarized in Table 3. Patients with severe disease often have a shorter incubation period (eg, ≤5 days) than those with milder disease. (60) Symptoms associated with RMSF evolve during the illness. (24)(47)(48) Early symptoms of RMSF (24)(47)(48) are observed during the first 1 to 4 days of illness. (55)(56) A rash usually appears a few days after the onset of symptoms, but most patients seek medical attention before the rash appears. (57)(58)(59) Most patients do not have the classic triad of a reported tick bite, fever, and rash at the time they initially present for medical attention. (55)(57) The rash associated with RMSF also evolves over time. (24)(47)(48) Classically, the rash begins as small, pink, blanching macules. Over the ensuing days, the rash usually becomes maculopapular, and there may be central petechiae. A petechial rash occurs relatively late (ie, at or after day 6

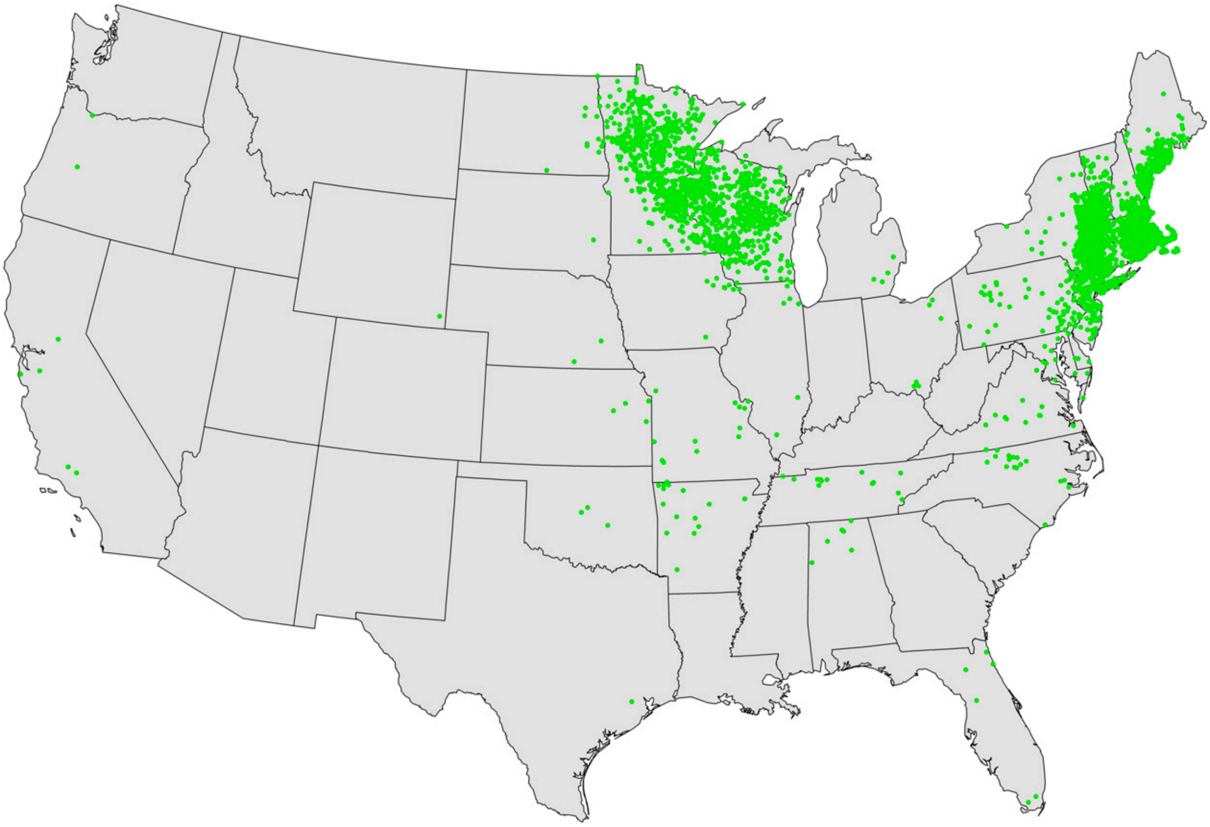

Figure 4. Anaplasmosis cases reported to the Centers for Disease Control and Prevention, 2016. (Reprinted with permission from Centers for Disease Control and Prevention. *Tickborne Diseases of the United States*. 5th ed. Atlanta, GA: Centers for Disease Control and Prevention; 2018.)

of illness) and indicates an advanced infection. The absence of a rash does not preclude the diagnosis of RMSF (less than half of patients do not have a rash during the first 3 days of illness, and some patients do not ever develop a rash). (55)(57) Children younger than 15 years are more likely to have a rash and are more likely to develop a rash sooner than are older individuals. (55)(61)(62) Untreated RMSF can have severe clinical manifestations, and progression to severe disease can be rapid, even in previously healthy individuals. Late clinical manifestations of RMSF are more severe. (63)(64) Patients who are treated early in the infection may have only mild disease with relatively rapid resolution of symptoms. (24)(47)(48) The highest incidence of RMSF is in older individuals (60–69 years of age), although RMSF occurs in people of all ages. (49) Children younger than 10 years have the highest RMSF case fatality rate. (49) Significant long-term sequelae have been described in patients with severe RMSF, including cognitive impairment, blindness, and peripheral neuropathy. (61)(65)(66)(67)(68)(69) Laboratory values in patients with RMSF (57)(70)(71)(72) are often within normal limits or only slightly abnormal early in the infection. Laboratory abnormalities are more likely to be observed as the infection progresses. Damage to the vascular endothelium by *R rickettsii* results in increased capillary permeability with widespread microhemorrhage and platelet consumption. (71) Hypovolemia leads to appropriate secretion of antidiuretic hormone with resultant hyponatremia. (72)

Diagnostic assays for RMSF are summarized in Table 4. (24)(47)(48) The diagnosis of RMSF must be a clinical diagnosis (based on the patient's signs and symptoms) because treatment of a patient with suspected RMSF should be initiated as soon as the diagnosis is suspected; the diagnosis can be confirmed through laboratory testing. The gold standard for the laboratory diagnosis of RMSF is the IFA assay. Other diagnostic assays used to confirm the diagnosis of RMSF involve detection of the organism's DNA (through a PCR assay) or visualization of the organism through immunohistochemical staining of a biopsy specimen (skin or other tissue). (24)

Treatment of RMSF is summarized in Table 4. (24)(47)(48) As soon as RMSF is suspected, therapy with

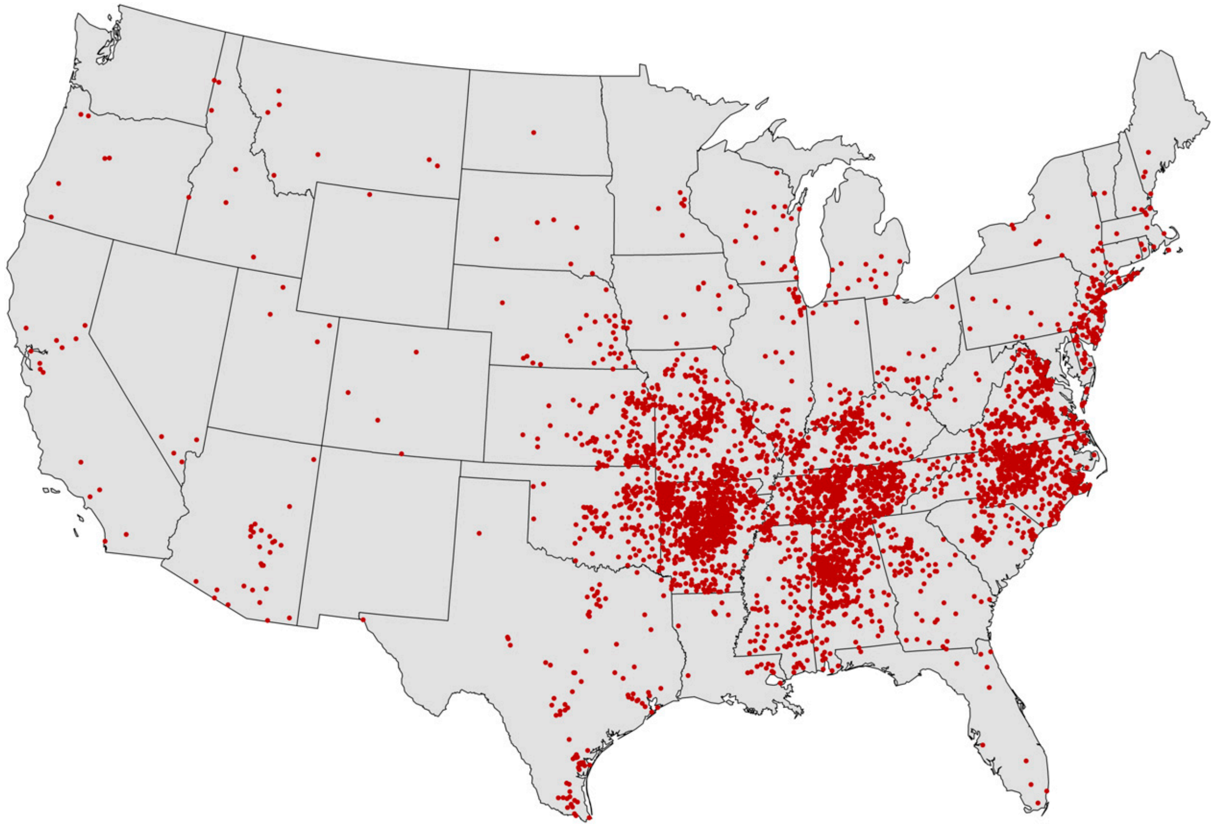

Figure 5. Spotted fever rickettsiosis (including Rocky Mountain spotted fever) cases reported to the Centers for Disease Control and Prevention, 2016. (Reprinted with permission from Centers for Disease Control and Prevention. *Tickborne Diseases of the United States*. 5th ed. Atlanta, GA: Centers for Disease Control and Prevention; 2018.)

doxycycline should be initiated. Initiation of treatment within the first few days of illness is associated with greater effectiveness (in terms of preventing mortality and decreasing morbidity) than if treatment does not begin until after the fifth day of illness. Doxycycline is the antibiotic of choice for all age groups for the treatment of RMSF.

BABESIOSIS

Between 2011 and 2016, 9,631 cases of babesiosis were reported in the United States. (73) In 2015 alone, there were 1,804 confirmed cases of babesiosis in the United States, primarily in New England and the mid-Atlantic area. (74) Table 2 summarizes characteristics of the causative organism (*Babesia microti* is the most common cause of babesiosis in the United States, but several other genetically distinct *Babesia* species exist [2]). *Babesia* species belong to the phylum Apicomplexa, which includes *Plasmodium* and other species. (75) The major cell target of these intracellular organisms is the red blood cell. (2)(73)(74)

Although *Babesia* infections can be transmitted through blood transfusion and congenitally, (73)(74) babesiosis is a primarily vector-borne disease. The vector for transmission of *B microti* is the blacklegged tick (*I scapularis*). (73)(74) Fig 1 shows the appearance of this tick. The white-footed mouse (*Peromyscus leucopus*) is the primary reservoir host for *B microti* in the United States. (74) Although not a reservoir host for *B microti*, the white-tailed deer (*Odocoileus virginianus*) can serve as a host for blood meals by the tick. (74) During the past several years, the increase in the deer population in some regions, including suburban areas, is likely related to the spread of the tick vector. (73) The seasonality of vector-borne transmission of *B microti* is summarized in Table 2 (73)(74). *B microti* infections have been acquired in the northeast as well as in the upper Midwest (76)(77)(78)(79) (Table 2, Fig 6). Occasionally, cases of babesiosis caused by other *Babesia* species have occurred in different parts of the United States, (80)(81) but the tick vectors and the reservoir hosts for these organisms are usually not known. (74)

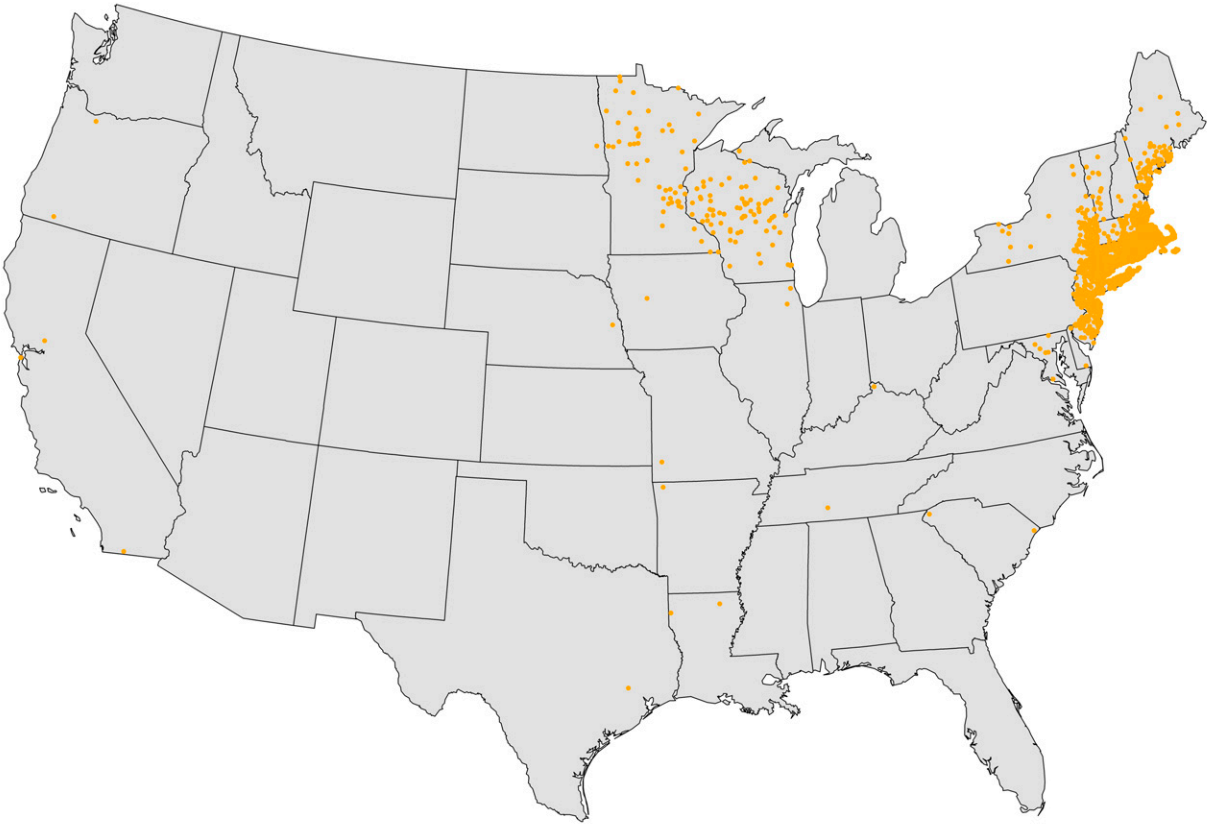

Figure 6. Babesiosis cases reported to the Centers for Disease Control and Prevention, 2016. (Reprinted with permission from Centers for Disease Control and Prevention. *Tickborne Diseases of the United States*. 5th ed. Atlanta, GA: Centers for Disease Control and Prevention; 2018.)

The incubation period and clinical manifestations of, and laboratory abnormalities associated with, babesiosis are summarized in Table 3. (2)(73)(74) In patients with symptomatic babesiosis, clinical manifestations usually develop within weeks of exposure, although manifestations may not develop until months after initial infection. (73) Parasitemia may persist, both in treated and untreated patients, and, especially in immunocompromised individuals, may result in recrudescence weeks or months later. (73)(82)(83) Even asymptomatic individuals can have persistent (eg, for more than a year) parasitemia. (74) Although babesiosis is often asymptomatic or associated with mild and nonspecific symptoms, it can manifest as a severe, potentially fatal disease. (73)(74) An estimated 50% of children with babesiosis are asymptomatic or have only a mild viral-like illness. (84)(85)(86)(87) Severe presentations are more likely if the patient is elderly and/or immunocompromised (eg, asplenic). (73)(74)(88)(89)(90) The first report of a case of human babesiosis in 1957 was in an asplenic patient. (91) The clinical manifestations of babesiosis (2)(73)(74)(79)(80)(81)(85)(88)(89)–(90)(92)(93)(94)(95) may resemble those of malaria. Although fever is common in patients with babesiosis, individuals at the extremes of age (eg, infants, the elderly) or those who are immunocompromised may be afebrile. (74) Organ failure and death may occur with severe infection. (73)(74)(88)(93) Hemolytic anemia and an elevated reticulocyte count are the most prominent laboratory abnormalities with babesiosis. (2)(73)(88)(93)(95)

Because the clinical manifestations of babesiosis are nonspecific, confirmation of the diagnosis requires laboratory testing. (2) The most reliable diagnosis of babesiosis is made in patients with the following 3 characteristics: 1) positive laboratory test results for *Babesia*, 2) residence in or travel to an area where *Babesia* is endemic, and 3) a viral infectionlike illness. (2) Diagnostic assays for babesiosis are summarized in Table 4 (73)(74). The first method of diagnosis of babesiosis is the identification of intraerythrocytic *Babesia* parasites by microscopic examination of Giemsa- or Wright-stained peripheral blood smears (73)(74) in patients with acute, symptomatic infection; the "tetrad" (Maltese cross) form is pathognomonic. (73)(74) Other methods of diagnosis of babesiosis are PCR analysis (73)(74)(96) and

Babesia-specific antibody detection through indirect fluorescent antibody assay. (73)(74)(97)(98)

Treatment of babesiosis is summarized in Table 4. (73)(74) Treatment for asymptomatic individuals is not recommended, irrespective of laboratory assays positive for *Babesia*. (2) If an asymptomatic individual has 1 or more positive *Babesia* assays, the assays should be repeated, and treatment should be considered if parasitemia continues for more than 3 months. (2)(73) Treatment is recommended for active babesiosis (viral infection–like symptoms with either visualization of *Babesia* parasites on a blood smear or a positive PCR assay for *Babesia*). (2) Symptomatic individuals with positive *Babesia* serology assays but no parasites observed on blood smears and no positive PCR assays for *Babesia* should not be treated. (2) Treatment for patients with active babesiosis usually entails combination therapy for 7 to 10 days with either atovaquone plus azithromycin or clindamycin with quinine. (2)(73)(74)(75) A longer duration of therapy may be necessary in patients with severe disease or those who are persistently symptomatic until parasitemia resolves. (2) The regimen of choice for the treatment of mild babesiosis in children is oral atovaquone with azithromycin. (73)(74) Severe babesiosis (eg, with parasitemia greater than 10%, or those with severe hemolysis, or hepatic, renal, or pulmonary compromise) is usually treated with intravenous clindamycin with quinine. (2)(73)(74) Severely ill patients may require or benefit from other concomitant interventions, such as mechanical ventilation, dialysis, and exchange transfusion. (73)(74)(99) With mild-moderate babesiosis, clinical improvement within 48 hours and complete resolution of symptoms within 3 months of initiation of therapy should occur. (2) Patients with moderate to severe babesiosis should be monitored carefully during treatment for improvement in clinical and laboratory parameters and decrease in parasitemia. (2) For example, with severe babesiosis, daily or every-other-day monitoring of the hematocrit value and the percentage of parasitemia until the patient has improved and the parasitemia has decreased to less than 5% is recommended. (2) Persistent low-grade parasitemia may occur for months after initiation of antimicrobial therapy. (2) If blood smears or PCR assays for *Babesia* remain positive for 3 months or more after initial treatment, repeated treatment should be considered. (2) For patients with especially severe or persistent symptoms despite appropriate treatment, the possibility of co-infection with other organisms with the same tick vector (*B burgdorferi* and/or *A phagocytophilum*) should be considered. (2) Special treatment considerations for severely immunocompromised patients (74) include 1) a duration of therapy of at least 6 weeks, with negative blood smears for at least 2 weeks before treatment discontinuation, and 2) treatment with higher doses of oral azithromycin.

PREVENTION

Prevention of acquisition of tick-borne diseases entails primarily preventing tick bites and removing ticks as quickly as possible if attachment has occurred. (100) To prevent tick bites, the following practices can be instituted: use of an Environmental Protection Agency–registered insect repellent (http://www.epa.gov/insect-repellents), treating cats and dogs for ticks, checking for ticks daily, and showering or bathing soon after outdoor exposure. Environmental Protection Agency–registered insect repellents contain compounds such as DEET (N,N-diethyl-meta-toluamide). In addition to applying such an insect repellent to the skin, clothing and gear (eg, boots) can be treated with products containing permethrin. Treatment of household pets (dogs and cats) for ticks should be performed under the guidance of a veterinarian. When checking for ticks, it is especially important to check in the following areas: around the hairline and scalp, in and around the ears, behind the knees, between the legs, around the waist, and inside the umbilicus. Any tick found attached to the skin should be removed as soon as possible and, after removing the tick, the skin should be cleaned.

In general, antibiotic drug prophylaxis after a tick bite to prevent tick-borne diseases is not recommended. However, for one tick-borne disease, Lyme disease, antibiotic drug prophylaxis can be implemented if a tick bite has occurred. (100) A single dose of doxycycline for the prevention of Lyme disease could be administered to children (5): 200-mg dose (or 4.4 mg/kg for children weighing <100 lb [<45.4 kg]), if the following conditions are met (100): 1) the patient resides in or has traveled to a state highly endemic for Lyme disease (Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, Wisconsin); 2) the attached tick is an adult or nymph stage *I scapularis* tick; 3) the estimated duration of attachment is at least 36 hours; 4) prophylaxis can be initiated within 72 hours of tick removal; and 5) the patient has no contraindication to doxycycline.

Summary

- In general, the epidemiology of tick-borne diseases reflects the characteristics of the specific tick vector, including the tick's known geographic distribution and seasonality. However, some tick-borne diseases are transmitted through other mechanisms (eg, congenital). Because of this, and in areas with high endemicity, there may be year-round incident "tick-borne" diseases.
- However, the epidemiology of tick-borne diseases in the United States is evolving, with new species being identified and the range of the tick vectors expanding. Although the most common clinical manifestations of and laboratory abnormalities associated with each tick-borne disease are known, not every infected individual has all such clinical manifestations or laboratory abnormalities with a given tick-borne disease, and the number and combination of clinical and laboratory findings experienced varies from one patient to the next. The possibility of concomitant tick-borne diseases (eg, *I scapularis* ticks transmit Lyme disease, *B miyamotoi* infections, anaplasmosis, and babesiosis) should be suspected if a patient's clinical or laboratory features are more severe than usually observed with a given tick-borne disease. Because tick-borne diseases can be fatal, and because a delay in the initiation of treatment can be associated with a poorer prognosis, the diagnosis may be based on clinical suspicion alone (while confirmatory laboratory studies are pending). Diagnostic laboratory testing for tick-borne diseases is evolving toward assays with faster turnaround times and less dependence on acute and convalescent serology samples. Prevention of tick-borne diseases primarily involves avoiding exposure to ticks and tick bites, checking for attached ticks, and prompt removal of ticks if found attached to the skin. Lyme disease remains the only tick-borne disease for which antibiotic drug prophylaxis is recommended for certain patients known to have an attached tick.

References for this article are at http://pedsinreview.aappublications.org/content/40/8/381.

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1. A previously healthy 9-year-old girl presents to the office in July with an enlarging, red, nontender, and nonpruritic rash of her left thigh for the past 3 days. She has felt warm, and her mom noted an oral temperature of 100.8°F (38.2°C) today. She has also complained of being achy and having a headache. A tick was removed from the site of the rash 14 days ago. The family lives in rural Maine. She and her family traveled to Tennessee for 1 week 6 weeks ago. On examination she is afebrile and her vital signs are normal. There is an annular, 8-cm-diameter erythematous macular lesion on her left thigh without central clearing, eschar, or drainage. Her mother states that she is allergic to amoxicillin because she had a rash when she was an infant. Which of the following is most likely responsible for the transmission of her illness?
   - A. *Amblyomma americanum.*
   - B. *Dermacentor andersoni.*
   - C. *Dermacentor variabilis.*
   - D. *Ixodes scapularis.*
   - E. *Rhipicephalus sanguineus.*
2. For the patient in question #1, which of the following is the most appropriate next step in management?
   - A. Begin cephalexin therapy.
   - B. Begin doxycycline therapy.
   - C. Obtain a blood sample for *Borrelia burgdorferi* polymerase chain reaction (PCR).
   - D. Obtain a serum sample for enzyme-linked immunosorbent assay *B burgdorferi* antibodies.
   - E. Obtain a serum sample for Western blot *B burgdorferi* immunoglobulin (Ig) G and IgM antibodies.
3. A 17-year-old boy is seen in the office for follow-up of 2 months of fatigue that started in November. He also complains of headache 1 to 2 times per week. He has not had weight loss, arthritis, arthralgias, or rash. He states that he feels warm occasionally but when he checks his temperature it is normal. He removed a tick from his inguinal region 7 months ago and did not develop a rash at the site. He lives in Oklahoma with his family, and his only travel was a Caribbean cruise the previous summer. His mother is concerned that he has Lyme disease or some other tick-borne illness. His vital signs and physical examination findings are normal. A complete blood cell count, erythrocyte sedimentation rate, and hepatic transaminase levels are within normal limits. Which of the following is the most appropriate diagnostic test for tick-borne disease?
   - A. *Anaplasma phagocytophilum* PCR on blood.
   - B. *A phagocytophilum* IgG antibody on serum.
   - C. *B burgdorferi* antigen assay on urine.
   - D. *B burgdorferi* Western blot IgG and IgM on serum.
   - E. No tick-borne disease testing is recommended.

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4. A previously healthy 6-year-old girl presents to the office in June with a 3-day history of fever to a temperature of 103°F (39.4°C) and increasing malaise. She also complained of a headache the past day. Last night the parents noted a red rash on her arms and legs, which then spread to her trunk. The parents have not removed any ticks from the girl, but the mom removed a tick from her brother 2 weeks ago. The family lives on a farm in Arkansas and has 2 pet dogs. In the office her temperature is 102.3°F (39.1°C), heart rate is 124 beats/min, respiratory rate is 22 breaths/min, blood pressure is 98/60 mm Hg, and oxygen saturation is 97%. She is moderately ill appearing but not lethargic. Her examination is remarkable for a generalized erythematous, blanching macular exanthem that is more prominent on her hands, arms, feet, and legs and involves her palms and soles. There is no meningismus. A complete blood cell count, blood culture, comprehensive metabolic profile, urinalysis, and *Rickettsia rickettsii* IgG and IgM immunofluorescent antibody assay are pending. She is started on empirical intravenous ceftriaxone therapy. Which of the following is the most appropriate additional antimicrobial therapy?
   - A. Atovaquone and azithromycin.
   - B. Chloramphenicol.
   - C. Ciprofloxacin.
   - D. Doxycycline.
   - E. No additional antimicrobial therapy is needed pending laboratory results.
5. A 12-year-old boy presents to the office in August with a 2-day history of low-grade fever, headache, and generalized myalgia. Three days before the onset of fever he had anorexia and increasing fatigue. He lives in New York City. He went to upstate New York 3 weeks ago for a 3-day camping trip and removed a tick from behind his right ear. He never developed a rash at that site. Laboratory testing is remarkable for hemolytic anemia, an elevated reticulocyte count, mild thrombocytopenia, and elevated hepatic transaminase levels. Which of the following is most likely to confirm the diagnosis?
   - A. Acute and convalescent *R rickettsii* immunofluorescent antibody assay IgG serum antibody.
   - B. Blood for *B burgdorferi* PCR.
   - C. Blood for *Ehrlichia chaffeensis* PCR.
   - D. Manual review of Wright-stained peripheral blood smear.
   - E. Urine for *B burgdorferi* antigen.

Tickborne Diseases in Children in the United States

Jennifer S. Read

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How Young Children Learn Language and Speech

Heidi M. Feldman, MD, PhD*

**Department of Pediatrics, Stanford University School of Medicine, Stanford, CA*

Practice Gaps

To prevent delays and provide effective clinical care to children with disorders of language and speech, pediatric clinicians must become familiar with prevailing theories, evidence, and recommendations of professional organizations. Pediatricians should not postpone evaluation or treatment of language and speech delays for boys, children from bilingual environments, second- or third-born children, or children with chronic otitis media with effusion.

Objectives

After completing this article, readers should be able to:

1. Apply current theories regarding how young children learn language and speech to accomplish primary prevention of language and speech disorders.
2. List key milestones of typical language development and indicators of high-risk status for language or speech disorders to assist in early detection of disorders.
3. Justify the use of both general and autism-specific screening tools for screening language and speech disorders.
4. Discuss primary and secondary causes of language and speech disorders to develop strategies for secondary prevention.
5. Evaluate the intensity and nature of speech-language pathology therapy to treat children with language and/or speech disorders as part of secondary and tertiary prevention.

Abstract

Pediatric clinicians are on the front line for prevention of language and speech disorders. This review uses prevailing theories and recent data to justify strategies for prevention, screening and detection, diagnosis, and treatment of language and speech disorders. Primary prevention rests on theories that language learning is an interaction between the child's learning capacities and the language environment. Language learning occurs in a social context with active child engagement. Theories support parent education and public programs that increase children's exposure

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ABBREVIATIONS

AAC	assistive and augmentative communication
SLI	specific language impairment
SES	socioeconomic status

to child-directed speech. Early detection of delays requires knowledge of language milestones and recognition of high-risk indicators for disorders. Male sex, bilingual environments, birth order, and chronic otitis media are not adequate explanations for significant delays in language or speech. Current guidelines recommend both general and autism-specific screening. Environmental and genetic factors contribute to primary language and speech disorders. Secondary and tertiary prevention requires early identification of children with language and speech disorders. Disorders may be found in association with chromosomal, genetic, neurologic, and other health conditions. Systematic reviews find that speech-language therapy, alone or in conjunction with other developmental services, is effective for many disorders. Speech-language interventions alter the environment and stimulate children's targeted responding to improve their skills.

INTRODUCTION

Learning language seems like a monumental task for the young child. The world's languages contain thousands of words that can be combined to convey an infinite number of meanings. Children are born without knowing which of the world's languages they must learn. If born in Brazil, they must learn Portuguese; if born in the Philippines, they must learn Tagalog. If born in Belgium or Quebec, or into an immigrant or refugee family, they may need to learn 2 different languages simultaneously. Despite these challenges, most children acquire the fundamentals of language effortlessly in the toddler and preschool years, without formal instruction or explicit feedback. By age 5 years, they have a vocabulary of thousands of words; create sentences with complex grammatical features; differentiate literal from nonliteral meanings, such as humor or metaphor; observe the social conventions of conversation; and apply language skills in the service of learning to read. By age 8 years, their speech sound inventory is mature.

Variation in the rate and efficiency of language development is substantial. Approximately 16% of children experience delays in the initial phases of language learning, and approximately half of those children show persistent difficulties. (1) In children age 3 to 5 years, speech and language impairment is the most prevalent eligibility criterion that warrants enrollment in special education preschool services (Fig 1). (2) Among school-age children, the category of learning disabilities, often a late manifestation of language and speech disorders, predominates as the eligibility criterion for special education; however, speech-language impairment ranks second. Deficits in language or speech that are sufficiently severe to interfere with daily functioning, including learning, communication, and/or social interactions, meet the criteria for a disability.

Pediatric clinicians are on the front line for primary, secondary, and tertiary prevention of language and speech disorders. (3) Primary prevention, such as immunizations, prevents the condition from ever occurring. Secondary prevention requires early detection and treatment of a disorder to result in a milder variant than would have

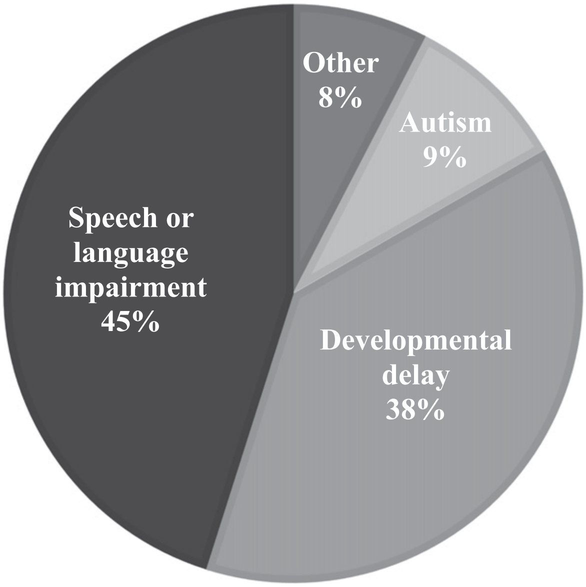


Figure 1. Among the more than 750,000 children in the United States age 3 to 5 years in 2016 who were enrolled in special education services, this pie chart shows the percentages found eligible for services based on speech-language impairment, autism, developmental delays, and other criteria. Speech-language impairment is the most common reason that children are deemed eligible for preschool special education services.

occurred otherwise. Tertiary prevention may not change the disorder but improves functional outcomes of affected children. The overriding objective of this review is to empower pediatric clinicians with prevailing theories, recent evidence, and recommendations to be used to promote primary, secondary, and tertiary prevention of language and speech disorders.

DEFINITIONS

Language is the distinctly human form of communication that binds human social groups. Language uses arbitrary but socially agreed on signals (words and sentences) in a rule-governed system to convey meaning. Unlike animal communication, human language uses signals creatively to communicate beyond the here and now, allowing discussion of past or future events and abstract, hypothetical, or imaginary ideas. Speech is the usual output of the language system, created by the complex and coordinated movements of respiratory, laryngeal, velopharyngeal, and oral structures. Other outputs include sign languages and written languages. Language is subdivided into receptive (ability to understand) and expressive (ability to produce) components. Language is further thought to comprise interacting subsystems: phonology (the system of speech sounds), lexicon (vocabulary), syntax (grammar), semantics (meaning), and pragmatics (social aspects of language that consider the speaker and the context). Speech is also composed of subsystems: articulation (speech sounds), voice and resonance, and fluency.

PRIMARY PREVENTION

Language learning is a product of the interaction between the child's learning capacities and the language environment. (4) Insights about how young children learn language derive from computer simulation models based on "parallel distributed processing" or "connectionist frameworks" that are designed to mimic characteristics of human brain structure and function. (5) Basic processing units in these models are simple and highly interactive, analogous to neurons in the brain. Units that become active simultaneously develop connections, and connections that occur in unison form networks. Knowledge is conceptualized as patterns of activity within the network; learning represents changes in the patterns of activity within and across networks. Importantly, networks do not require any initial biases or built-in organization to become organized. Rather, they organize based on experiences in the environment. These models can explain how infants learn whatever language they are exposed to. These models have also been found to further explain many of the phenomena of language learning, such as how children learn to correctly conjugate both regular verbs and irregular verbs. (5)

A challenge for the infant is segmenting the sound stream into meaningful units, such as words, that serve as inputs for learning. Children use "statistical learning" for this purpose. Statistical properties of sound sequences vary. For example, sounds that occur within words have a higher frequency of co-occurrence than sounds that occur between words. Infants as young as age 8 months unconsciously detect these distributional statistical properties and use them to segment the continuous sound stream into wordlike units. (6) Sequential statistical learning also allows the young child to detect sequential ordering and co-occurrence of words within sentences to explain the acquisition of syntax. (7) Moreover, infants and children can take advantage of statistics of word referent co-occurrences to learn the meanings of words. (8) Statistical learning is facilitated when parents use child-directed language, colloquially known as *baby talk*. Child-directed language is characterized by limited vocabulary, short sentences, multiple repetitions, relatively few errors, and exaggerated intonation. (9)

An important ingredient for language learning is the social context. Early language learning requires human interactions; televisions and computers are not sufficient. Warm, mutually respectful, low-stress exchanges between infants and competent language users (adults or other children) facilitate learning. Language learning requires the child's active engagement with the input. Children must monitor the input, detecting, for example, differences between what they heard and what they might have said or what they thought a word meant. Recognition of the discrepancy helps children progress in learning semantics and syntax. Talking about what a child is doing or expanding what a child has just said facilitates the child's active engagement.

Another challenge for the infant is learning to map speech perception to speech production. (10) Most of the structures that generate speech sounds in the vocal tract are hidden from view. "Mirror neurons" that fire both when an individual performs an action and when the individual perceives others performing the same action are plausible mechanisms for linking perception to production. Human mirror neuron populations seem to be clustered in several cortical areas in the brain, including the prefrontal cortex, that are often implicated in language use. (10)

Primary prevention of language and speech delays or disorders may be achieved by providing children with a rich language environment within positive social relationships. Therefore, recommendations that primary care clinicians can give to parents of infants and young toddlers are as follows:

- Speak often to infants and young children. Baby talk—the use of simple sentences with exaggerated intonation—is well suited to children's learning needs.

- Use language to describe or explain what a young child is doing or to expand what a child has just said to engage the child for language learning.
- Use language during social interactions, such as reading books and playing. Reading is associated with more language input than meals, baths, or play. (11)
- Limit screen time (12) in favor of active social interactions.
- Support public policy initiatives that provide education to parents about language learning, such as nurse home visiting programs, or that support effective language environments for children, such as publicly funded universal preschools.

Reach Out and Read (http://reachoutandread.org/) is a program for primary care offices that provides books to families and counseling on the importance of reading to children. It represents a strategy for modeling as well as counseling on the importance of language and reading.

EARLY DETECTION OF LANGUAGE AND SPEECH DELAYS

Early detection of language and speech delays is predicated on knowledge of the pattern of development. Table 1 documents milestones in the development of language and speech from infancy to age 8 years. Children produce their first words at approximately age 1 year. Initial lexical growth is slow, approximately 1 to 2 words per week. Once the vocabulary reaches approximately 50 words, the pace of development accelerates. Lexical growth increases to 1 to 2 new words per day, and children begin combining words into 2-word phrases. The "vocabulary spurt" has been attributed to biological factors, such as myelination of white matter language pathways. (13) An increase in the pace of learning also conforms to self-organization of a neural network. (5) Between ages 2 and 4 years, children build their lexicon and grammatical skills. Patterns of development vary across children, most likely as a function of their experiences in the environment. By school age, all of the fundamentals of language are typically mastered. Children may still show immaturities in motor speech skills to age 8 years, but intelligibility at school age should be approximately 100%.

Developmental surveillance may detect children at high risk for disorders in language and speech. Surveillance uses all clinical approaches (history, physical and neurologic examinations, observations) at all health supervision visits. "Red flags" (Table 2) are delays or differences that indicate a high prevalence for persistent disorders, and they should prompt an evaluation.

The American Academy of Pediatrics recommends developmental screening with a validated instrument at least at ages 9, 18, and 24 to 30 months. (14)(15) Screening establishes whether a nonsymptomatic or presymptomatic child is at high or low risk for a language or speech disorder. A 2-step screening process is important. The first step should use a general screening instrument, such as the commercially available Parents' Evaluation of Developmental Status (http://www.pedstest.com/) or Ages and Stages Questionnaires, Third Edition (http://agesandstages.com/products-services/asq3/), or other tools that have been developed for use in low- and middle-income countries. (16)(17) The second screen establishes the risk of autism spectrum disorder using an instrument such as the Modified Checklist for Autism in Toddlers, Revised with Follow-up. (18) Both screens are important. Autism screening alone may not be sufficient for establishing risk of language and speech disorders, which are more prevalent than autism (Fig 1). Autism screening may detect some children missed on global screens.

Screening is not necessary when the child is known to have delays; has another condition associated with language or speech disorder, such as hearing loss or preterm birth (see later herein); or is enrolled in therapy for language or speech. In such cases, further description of the child's strengths and difficulties may be useful for monitoring the child's progress. The following commercially available instruments could be used in such situations in the clinical setting:

- MacArthur-Bates Communicative Development Inventories (https://mb-cdi.stanford.edu/), parent-report instruments for children age 8 to 37 months.
- Language Development Survey (http://www.aseba.org/?s=Language+Development+Survey&id=m), a parent-report instrument for children age 18 to 35 months.
- The Clinical Linguistic and Auditory Milestone Scale of The Capute Scales (http://www.brookespublishing.com/resource-center/screening-and-assessment/the-capute-scales/), a combination of direct assessment and parent report for children birth to 36 months old.
- Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist (http://brookespublishing.com/wp-content/uploads/2012/06/csbs-dp-itc.pdf), a direct assessment of social communication for children age 6 to 24 months and useful for children who may have autism.

VARIATIONS IN LANGUAGE AND SPEECH DEVELOPMENT THAT DO NOT TYPICALLY CAUSE DELAY

Boys may show mild delays in the development of language and speech skills compared with girls. (19) However, among typically developing children, the differences are relatively small and not clinically relevant. Boys have higher rates of language and speech

TABLE 1. **Key Milestones in the Development of Receptive and Expressive Language and Speech**

AGE	RECEPTIVE SKILLS	EXPRESSIVE SKILLS	SPEECH
Newborn	• Attends to voice • Regards face	• Cries	
3 mo	• Smiles when spoken to	• Differentiates cry • Coos (makes vowel-like musical sounds) • Coos reciprocally with an adult	
6 mo	• Turns when name is called	• Begins to babble (adds consonant sounds, such as *b, d, m*)	
9 mo	• Stops when told "no" • Learns routines, such as "wave bye-bye"	• Points to wants or to interesting objects or actions • Says *mama* or *dada* nonspecifically	
12 mo	• Follows simple commands with gestures	• Says *mama* or *dada* specifically • Jargons (strings of babble that sound like speech) • Says first words	
15-18 mo	• Points to body parts • Follows single command without gesture	• Acquires words slowly • Uses simple and idiosyncratic forms • Participates in conversations	
18-24 mo	• Understands sentences	• Exhibits vocabulary of ≥50 words • Learns new vocabulary items easily • Uses 2-word phrases	• 50% correctly use *p, m, h, n, w, b*
24-36 mo	• Follows 2 and 3-step commands • Answers "wh-questions"	• Uses >2-word phrases • Uses increasing complex grammar, such as negation, questions	• 50% correctly use *k, g, d, t, ng, f, y*
36-48 mo	• Understands plurals, pronouns, and possessives • Understands questions of "who", "why," and "how many"	• Combines 3–4 words in a sentence • Uses conjunctions, such as *and, or, but*	• 90% correctly use *p, m, h, n, w, b* • 50% correctly use *r, l, s, ch, sh, z* • Able to produce final consonants in words such as *bus* • No longer replaces sound made in the back of the mouth (*g, k*) with sounds made in the front of the mouth (*d, t*)
48-60 mo	• Understands concepts, such as same/different	• Uses mature grammar at near-adult levels • Constructs narrative discourse, such as tells or retells stories, makes explanations	• 50% correctly use *j, v*, voiceless *th (thing)* • 90% correctly use *k, g, d, t, ng, f, y* • Correct production of consonant clusters, such as *st* in *stop* • No longer deletes weak and unstressed syllables, such as in *banana*
60-84 mo	• Limited by the child's conceptual knowledge, not language skills • Understands humor, metaphor	• Mature language constructions • Increasing use of sophisticated vocabulary and complex grammar	• 90% correctly use *r, l, s, ch, sh, z, j, v, th* • No longer substitutes liquids (*r, l*) with glides (*w, j*) • Can correctly use fricatives, such as voiceless *th*

disorders than do girls. Therefore, the probability that a boy with an early delay will develop a disorder is high.

Children raised in bilingual environments are capable of learning 2 languages at the same time, (20) even children with disabilities such as Down syndrome. (21) Bilingual children may have smaller vocabularies in each of their languages than monolingual children, although their combined vocabulary should be comparable in size to that of monolingual children. (22) They may initially show mixing of the 2 languages, although over time separation of the 2

TABLE 2. **Red Flags Indicating High Risk of Language or Speech Disorder and Prompting Evaluation**

AGE	RED FLAG OR INDICATION FOR REFERRAL FOR EVALUATION
Any age	Failure to participate freely and frequently in social interactions
6 mo	Lack of ability to laugh, vocalize, respond to sound, participate in reciprocal vocal interactions
9 mo	Failure to respond differentially to name or to produce babble (such as *baba, dada*)
12 mo	Inability to point to objects or actions Lack of use of gestures, such as shaking head "no" Inability to participate in verbal routines, such ability to wave to "wave bye-bye" No use of *mama* or *dada* specifically for a parent
18 mo	<5 words beyond *mama* and *dada* Failure to follow simple commands with gestures
24 mo	Vocabulary <50 words No 2-word combinations <50% of utterances intelligible to unfamiliar adults
36 mo	Inability to follow simple directions without gestures No ≥3-word combinations <75% of utterances intelligible to unfamiliar adults
>36 mo	Loss of language and speech skills, particularly in the presence of regression in social abilities and in the absence of regression in motor skills

languages occurs. (22) Bilingual exposure is not a full explanation of language or speech delays. Bilingual children have comparable risks of language disorders as monolingual children.

Another source of variation is the child's birth order. Later-born children are likely to hear less adult-generated language directed toward them but are more likely to overhear conversations between adults and their older siblings and have the older siblings as role models. (23) Overall, studies show that later-born children do not acquire language at a later age than do firstborns. Clinicians should use the same assessment and management approaches in the care of later-born children as they do with firstborn children with comparable delays.

Chronic otitis media with effusion does not cause developmental delays in language or speech. Randomized clinical trials comparing early tympanostomy tube placement with watchful waiting showed that the operation changed the duration of effusion and did not change the language outcomes in preschool- or school-age children. (24)(25) Chronic otitis media is more prevalent in situations that also put language learning at risk, including poverty, crowding, limited breastfeeding, and parental smoking, (26) suggesting that chronic otitis media may be a marker for adverse conditions that are associated with poor language or speech development. Clinicians should consider multiple reasons that children with chronic otitis media with effusion develop language or speech delays.

In summary, it is a misconception that children from the following categories with delays in early language or speech development will catch up to peers without any intervention: boys, children from bilingual homes, later-born children, and children with chronic otitis media with effusion. In all these cases, the same thresholds should be used to define delays and disorders, and the same clinical procedures should be followed when delays are detected.

LANGUAGE AND SPEECH DELAYS

The term *delays* implies that the development of language or speech skills is slower than expected for age and follows an usual developmental pattern. A delay becomes clinically relevant when the rate of development falls below 75% expected, such as when a skill expected at 18 months is not present in a 24-month-old child (18/24 = 3/4 or 75% the expected rate). Approximately half of all children who are delayed in language at age 2 years catch up by age 3 years. Children who show good symbolic play skills and/or normal receptive language despite delayed expressive language have a better prognosis than those with delays in symbolic play and receptive language. Children with either language or speech delay should receive a comprehensive pediatric evaluation. Table 3 describes the components of a

TABLE 3. **Evaluation of a Child with Language or Speech Delay or Disorder**

COMPONENT OF EVALUATION	CRITICAL INFORMATION
History	Age at onset, initial presentation, and subsequent course Affected subcomponents Effects of previous treatments
Medical history	Birth history Previous illnesses and chronic conditions
Review of systems	Associated signs and symptoms
Family history	Family members with language, reading, or intellectual disorders Other health conditions
Psychosocial factors	Primary caregivers, parent education Number in the household, financial resources, stress Nature of parent-child interactions Amount and quality of child-directed speech Out-of-home care, including child care, preschool, or school
Physical examination	Growth parameters Dysmorphic features Oral-motor structure and function
Neurologic examination	Structural abnormalities, such as asymmetry in tone or reflexes Functional disorders, such as seizures
Audiologic assessment	Ear-specific information or sound field testing
Cognitive skills	Developmental assessment or an intelligence test
Symptoms of autism	Social communication and restrictive or repetitive behaviors

comprehensive pediatric evaluation. Based on the results of that assessment, the clinician may refer the child for treatment or place the child on an enhanced surveillance schedule. Factors that cause language or speech delays and that should prompt treatment are described in the following subsections.

Environmental Factors

A recent systematic review found that family environmental factors, such as socioeconomic status (SES) and parental education, parental health, and the level of engagement of parents with children, are all associated with the rate of language development. (27) Variation in the amount of language a child hears may mediate the effect of adverse social conditions on development. The classic observation that social class affects language outcomes came from the work of Hart and Risley, (28) who estimated the number of words children heard by recording weekly samples of conversations in their homes. Children of low SES were exposed to an estimated 30 million fewer words than were children of high SES in the preschool years. Recent studies using daylong recordings of home language have confirmed that the amount of speech that children hear at age 16 or 18 months predicts lexical growth and speed of language processing at older ages. (11)(29) In interpreting these environmental influences on child language, it is important to recognize the possibility of shared genetic variance between parent and child. (30)

Infants raised in orphanages have profound delays in the development of language and speech, along with many other health and developmental disorders. (31) The Bucharest Early Intervention Project demonstrated that these devastating effects could be eliminated through placement in foster care before 15 months of age. Adverse effects were moderated through placement in foster care before but not after 24 months of age. (32) These encouraging data demonstrate the plasticity of language in its earliest stages.

Sex Differences

Boys have higher rates of language and speech delays and disorders than girls. (33) This finding may reflect genetic variation, implicating sex chromosomes. Male sex is associated with proinflammatory forces and placental lesions. (34) The maternal immune response against the invading interstitial trophoblast may be an initial event leading ultimately to sex differences in language disorders. Another possibility is that prenatal hormones, such as testosterone, exert important influences on the developing brain, influencing structural features such as the degree of laterality or difference between the left and right hemispheres. (35)

Biological factors interact with environmental factors to explain sex differences in language and speech. Girls prefer to remain in close proximity and to engage in social interactions with adults; boys prefer active, rough and tumble play. Sex differences interact with SES. Boy-girl sex differences have been found in low-SES but not high-SES children. (19) Clinicians are often slow to refer boys with language delays for treatment on the assumption that the child will eventually catch up. However, because boys are at higher risk than girls for disorders, as mentioned previously herein, clinicians should proceed to evaluation and treatment when a delay is detected.

Genetic Factors

Genetic variation seems to be important for variation in how quickly and efficiently children learn. (36) Disorders of speech and language cluster in families; the median incidence of language difficulties was found to be more than 3 times higher in families of children with language impairment than in unaffected families. (37) Twin studies have confirmed that concordance of speech and language disorders is higher in monozygotic pairs than it is in dizygotic twin pairs. The presence of reading disorders in the family also put children at risk for language disorders. (38)

The first reports identifying a specific genetic alteration associated with language and speech disorders came from studies of a large 3-generation family, called the KE family, in which approximately half of the members had complex speech difficulties. A single nucleotide change on a gene called *FOXP2,* located on chromosome 7q31, differentiated affected and unaffected family members. Curiously, this gene is one of a family of genes controlling transcription of other genes rather than a gene that codes traits. One theory is that *FOXP2* influences the expression of other genes, such as *CNTNAP2,* which encodes a neurexin and is expressed in the developing human cortex. Genetic variation in *CNTNAP2* has been associated with language impairment.

Beyond these findings, it has proved difficult to identify specific genes associated with language and speech disorders. (39) It is possible that multiple genes may be involved (40) or that despite behavioral similarities, the disorders are heterogeneous, each with a distinctive genetic etiology. Decisions about genetic testing for children with a speech and language disorder should be individualized, based on the phenotype, symptom severity, family history, and related factors.

PRIMARY DISORDERS OF LANGUAGE AND SPEECH

Secondary or tertiary prevention is predicated on early detection of language or speech disorders and prompt treatment because early treatment is generally associated with better outcomes than is delayed treatment. Language disorders represent deficiencies in the ability to express or understand human communication. Delays become disorders when they persist to school age, follow different developmental trajectories, are severe, and/or negatively affect functioning. One classification subdivides language disorders into receptive, expressive, and mixed expressive-receptive language disorders. However, this classification system may not be accurate. (41) Difficulties with language expression may be accompanied by limitations in language comprehension and processing that are subtle and more difficult to detect than the problems of expression. (41) An alternative classification of disorders of language is based on the aspects of language affected (Fig 2), aligned with subcomponents: phonological disorders, limited lexicon, syntactic disorder, semantic disorder, and pragmatic disorder. Speech disorders can also affect 1 or more subcomponents (Fig 2). Motor speech disorders include articulation disorder, dysarthria, and childhood apraxia of speech. Abnormal vocal quality and resonance may be hoarseness, hypernasal speech, or hyponasal speech. Disorders of fluency include stuttering and other dysfluencies.

A persistent and serious delay in the acquisition of language skills in the absence of other developmental, health, or mental health conditions goes by many names: spoken language disorder, primary language impairment, or specific language impairment (SLI). (42) In SLI, the language disorder is the most relevant finding, although associated conditions may also be present. SLI is clinically heterogeneous. Usually, difficulties with syntax are prominent (Fig 2). Other features may include delays in phonological development, semantics, and/or pragmatics. Children with SLI typically present with delayed emergence of single words, phrases, and sentences. Comprehension often seems to be relatively spared. Speech skills also may or may not be impaired.

Several general neuropsychological processes, such as speed of language processing and memory, are associated with SLI. Speed of language processing at age 18 months, as measured in an eye-tracking task, has been found to be associated with measures of language skills up to age 8 years. (43) Children who are late talkers at age 2 years and at high risk for SLI have slower speed of processing than children with typical early language. Slow speed of processing may result in SLI because affected children may have difficulty understanding, anticipating, and learning from

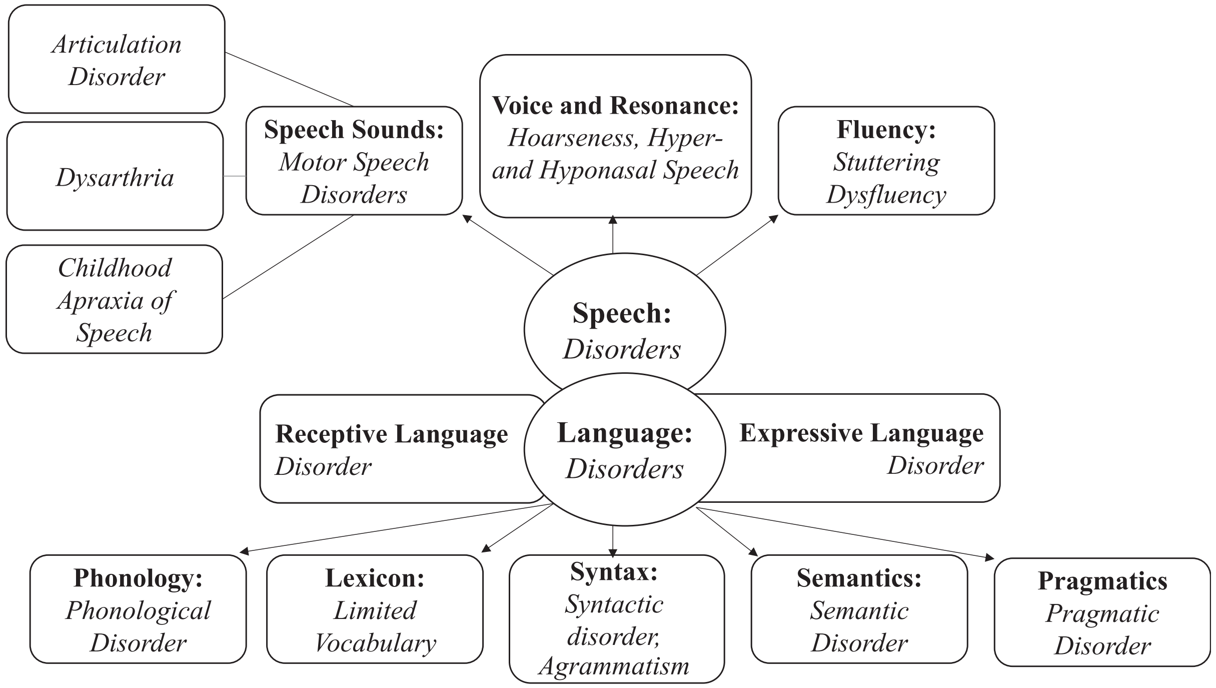

Articulation Disorder
Dysarthria
Childhood Apraxia of Speech
Speech Sounds: Motor Speech Disorders
Voice and Resonance: Hoarseness, Hyper- and Hyponasal Speech
Fluency: Stuttering Dysfluency
Speech: Disorders
Receptive Language Disorder
Language: Disorders
Expressive Language Disorder
Phonology: Phonological Disorder
Lexicon: Limited Vocabulary
Syntax: Syntactic disorder, Agrammatism
Semantics: Semantic Disorder
Pragmatics Pragmatic Disorder

Figure 2. Disorders of language and speech based on the affected subcomponent of the language or speech system. Bold indicates the domain of language or speech, and italics indicate the class of disorders.

speech presented at the usual rapid pace. Deficits in phonological short-term and working memory are also associated with SLI, (44) presumably because it is essential to hold sound patterns in mind in order to learn new words and structures. Phonological short-term memory can be measured by a nonword repetition task that requires children to listen to novel phonetic sequences of varying lengths and repeat them back. At older ages, children with SLI may meet the criteria for attention-deficit/hyperactivity disorder and/or may have difficulties with executive functions, such as response inhibition, working memory, organization, or planning. Children with SLI are at risk for later reading disorders because reading rests on a foundation of language abilities. (45)

Disorders of speech may occur in isolation or in conjunction with disorders of language. Articulation disorders are motor speech disorders that represent difficulties producing specific sounds of the language (Fig 2). Mild articulation disorders are highly prevalent and rarely disrupt communication or social functions. Severe articulation disorders may affect other domains of function. Dysarthria is a disorder of the muscle movements required for speech production and often occurs in the aftermath of brain injury. Childhood apraxia of speech is considered a disorder of planning and executing speech sounds. Hallmarks of the condition include delays in the onset of babbling or single-word productions, errors in articulating vowel sounds, inconsistent errors in producing words, increasing difficulty with words or phrases of increasing length, increased difficulty with production of spontaneous as opposed to well-rehearsed sentences, and effortful speech. The importance of differentiating childhood apraxia of speech from other disorders is that the treatment approach is distinctive; children typically require an approach that emphasizes motor programming and motor learning to improve production of speech sounds.

Stuttering is a disorder of fluency (Fig 2). Children often experience dysfluency before age 4 years as their thinking processes outpace their speech processes. Developmental dysfluency involves repetition of entire words or phrases. Stuttering is a nondevelopmental problem that includes repetition of individual speech sounds (*p-p-p-pop*); prolongations (*mmmme*); abnormal pauses between sounds; excessive use of fillers, such as *uh* or *um*; and use of behavioral strategies, such as self-slapping to try to get the words out. Even at ages younger than 4 years, the presence of the features of stuttering should prompt referral for further evaluation and treatment.

SPEECH-LANGUAGE DISORDERS SECONDARY TO KNOWN CONDITIONS

Early detection and treatment of language and speech disorders in children with other health or neurodevelopmental conditions is another strategy for secondary and tertiary prevention. The use of parent-reported questionnaires or direct observation language and speech instruments in pediatric subspecialty care is recommended for children, especially for those who are not receiving speech-language pathology services, early intervention, or special education (see previously herein). Recommendations for the evaluation of children with language and speech delays or disorders are designed to rule out known causes, including adverse psychosocial conditions (Table 2).

- *Hearing loss*. Language and speech disorders are highly likely with severe to profound hearing loss (threshold >55 dB). Individuals with mild (threshold of 26–40 dB) to moderate (threshold of 41–55 dB) sensorineural hearing loss may be able to detect and discriminate vowel sounds and low-frequency consonants, such as *m* and *b*, but may not detect or discriminate high-frequency consonants, such as *f, th,* and *sh*. Universal newborn hearing screening has increased early identification of children with moderate to profound hearing loss. Reevaluation of hearing in children with language or speech abnormalities is critical because the newborn test results may have been a false-negative, the hearing loss may be mild, or the child may have a progressive hearing loss.
- *Global developmental delay and intellectual disability*. Language and speech delay may be the initial presentation of children with global developmental delays. If delays persist and are accompanied by deficits in adaptive skills, children may meet the criteria for intellectual disability. Intellectual disability ranges from mild (IQ = 55–69) to profound (IQ < 25) levels. Language skills are generally commensurate with other developmental abilities. Even children with severe intellectual disability (IQ = 25–39) typically learn at least minimal language skills.
- *Autism*. Autism is defined by 2 key criteria: deficits in the domain of social communication and excessive restricted or repetitive behaviors. The presenting problem in autism is often delays or regression in speech and language skills. The prevalence of autism had been increasing in the past 2 decades and may have stabilized during the past 8 years. (46) Prognosis is better when children receive early intervention services than when behavior management and education are delayed. For these reasons, consideration of the diagnosis of autism is critically important in the evaluation of children with language delay.
- *Known genetic variations*. Chromosomal and genetic conditions have distinctive profiles in terms of speech and language. For example, in trisomy 21 or Down syndrome, deficits in speech and language skills are often more severe than deficits in nonverbal skills. In Williams syndrome, caused by a deletion on chromosome 7, deficits in nonverbal skills are more severe than deficits in language. Fragile X syndrome is caused by trinucleotide repeats and mutations in the *FMR1* gene. Individuals with fragile X syndrome have deficient language skills in association with poor social skills, high levels of anxiety, and frequent hyperactivity. Approximately 20% to 25% of individuals with fragile X syndrome meet the criteria for a diagnosis of autism.
- *Neurologic disorders*. Structural brain injuries may affect language and speech. Children with injury to the left or right hemisphere frontal and temporal regions may show delays in the early phases of language development and subsequent disorders, although their symptoms are milder than those of adults with similar injuries. (47)(48) Notably, environmental factors influence the rate of language learning after brain injury. By age 5 years, children from high-SES families with brain injury outperformed children without brain injury from low-SES families. (49) Functional magnetic resonance imaging studies have found that children with early left hemisphere injury show multiple pathways of plasticity associated with variation in outcome. (50) Specific epilepsy syndromes are associated with language and speech disorders. Landau-Kleffner syndrome is a rare seizure disorder associated with regression in speech and language skills and, therefore, is part of the differential diagnosis in autism with regression. However, whereas the regression in autism typically occurs before age 3 years, the regression in Landau-Kleffner syndrome occurs later. The cardinal finding is auditory agnosia, a profound disruption of language comprehension with resulting adverse effects on language production. Other neurologic conditions with effects on language and speech include tuberous sclerosis.
- *Cleft palate*. Cleft palate is failure of fusion of the hard and/or soft palate. Even if the defect is repaired, weak velopharyngeal muscles allow air to flow through the nose rather than out the mouth in the production of speech sounds, resulting in hypernasal speech. Children with cleft palate, even as an isolated condition and not part of a broader syndrome, may also experience delays or disorders in the development of language as well as speech although the reasons are not clear.
- *Other health conditions*. Meta-analyses show that children born preterm show persistent delays in the development of language, (51) independent of SES, and even among samples that include only children without

major disabilities, such as cerebral palsy, intellectual disabilities, and sensory impairments. (52) These deficits have been attributed to subtle neurologic deficits that may be present even in the absence of telltale signs on neuroimaging. Similarly, children with congenital heart disease show delays in the development of language associated with changes in white matter. (53)

MANAGEMENT AND TREATMENT

Children with language or speech delays or disorders have failed to learn language from observation and social participation. Therefore, watchful waiting is rarely a good approach. Therapy is warranted. The speech-language pathologist is the professional charged with designing and implementing the treatment plan for a child with language or speech delays or disorders. Speech-language pathology services alone may be adequate for the child with mild to moderate language or speech delays or isolated disorders without complications. Early intervention for children birth to 3 years old or special education services for children older than 3 years is appropriate for children with moderate to severe language and speech disorders, other developmental conditions, and/or behavioral challenges that compromise participation and cooperation. Referral to therapy services is appropriate even while the comprehensive evaluation of the disorder is ongoing because of the long delays for many diagnostic services.

Although the causes of language and speech disorders are diverse, including genetic or neurologic conditions, manipulation of the child's experience in the environment is the main lever available to improve the child's skills and functioning. The speech-language pathologist, implicitly or explicitly, creates environments that increase the odds of the child's learning the weak or missing skill. Effective language interventions may provide a higher number of effective language learning episodes than would be available to children in their typical environment. Therapy may increase the child's opportunities to listen and speak, increase the salience of elements that the child has not mastered, and/or encourage expression of weak and developing skills. Therapy may also provide corrective feedback, such as recasting, that facilitates learning correct forms. Critical ingredients for therapeutic intervention, analogous to primary learning, are the child's active engagement and a warm supportive relationship. Therapy for toddlers and preschool-age children is typically play-based rather than drill. The specific activities chosen for a session focus on interests of the child. Table 4 includes a link to an example of home-based speech-language therapy.

The data on the efficacy or effectiveness of speech and/or language therapy, especially using randomized controlled trials, is limited. However, a systematic review and meta-analysis found that speech and language therapy is generally effective for children with phonological or expressive vocabulary difficulties but less clear for children with expressive syntax difficulties. Little evidence was available considering the effectiveness of the intervention for children with receptive language difficulties. (54)

Children often get a minimal dose of speech-language therapy, such as 30 to 60 minutes of therapy a week or less. The low dose of treatment is driven in part by child factors, such as children's relatively weak attentional capacity, and by systems issues, such as high costs and limited availability of therapists. Participation of parents, family members, and teachers in the program leverages the otherwise limited intensity of service. A systematic review found no significant differences between interventions administered by trained parents and clinicians. (54) A second systematic review reported that home programs can lead to growth in a child's skills and are more effective than no intervention, provided that a high dose of the program is delivered by parents who have received direct training in the intervention techniques. (55) Another strategy to increase the dose of treatment is to provide group therapy sessions; the duration of treatment is not the 30 to 60 minutes reserved for a single child, but 2 to 3 hours for 4 to 8 children. The added advantage of group therapy is that children practice their developing skills with other children in seminaturalistic settings. A systematic review found no differences in the effects of individual versus group therapies. (42) Language and speech therapy are often part of a child's individual educational plan at school. Teachers as well as parents should know the goals and strategies that the speech-language pathologists are using and apply them in the classroom to maximize the effect of therapeutic services.

As children age, it becomes increasingly important that they can use language and speech skills in the service of functional domains, including learning, communication, and social interaction. A systematic review of school-based treatment procedures addressing social communication behaviors found that gains were seen in conversational abilities, including topic management skills, narrative production, and repairs of inadequate or ambiguous comments. (56)

For children with poor motivation or disordered behavior, behavioral measures may be included with rewards and consequences for desired and undesired behaviors, respectively. Behavioral approaches are typically required for children with autism who lack motivation to communicate.

TABLE 4. **Resources for Parents and Professionals**

TARGET	MEDIUM	TITLE AND SOURCE
Parents	Websites	• National Institute on Deafness and Other Communication Disorders Fact Sheet: "Your Baby's Hearing and Communicative Development Checklist": https://www.nidcd.nih.gov/sites/default/files/Documents/health/hearing/NIDCD-Hearing-Development-Checklist.pdf • Babyhearing.org: https://www.babyhearing.org/ • Center for Disease Control and Prevention FREE Milestone Tracker: https://www.cdc.gov/ncbddd/actearly/index.html • First Words Project, 16 Gestures by 16 Months: http://firstwordsproject.com/about-16by16/ • Tips for Parents of Preschoolers on Shared Reading: http://www.nea.org/assets/docs/HE/englishtips.pdf • Autismspeaks.org • Apraxia-kids.org
	Books	• Agin MC, Geng, LF, Nicholl MJ. (2003). *The Late Talker: What to Do if Your Child Isn't Talking Yet*. New York, NY: St Martin's Press • Eichten PI. (2000). *Help Me Talk: A Parent's Guide to Speech and Language Stimulation Techniques for Children 1 to 3 Years*. Glen Allen, VA: Pi Communication Materials • Feit D. (2007). *The Parents' Guide to Speech and Language Problems*. New York, NY: McGraw-Hill • Hulit LM, Fahey KR., Howard MR. (2015). *Born to Talk: An Introduction to Speech and Language Development*. Boston, MA: Pearson
Clinicians	Websites	• Information about developmental milestones and clinical indicators of autism available on the CDC's "Learn the Signs. Act Early" website: https://www.cdc.gov/ncbddd/actearly/index.html • American Speech-Language Hearing Association continuing education courses: http://www.asha.org/ce/ • The American Academy of Pediatrics Bright Futures: http://www.brightfutures.org • Autism Navigator for Primary Care: http://www.autismnavigator.com/ Examples of home-based speech-language pathology therapy: • Therapy for childhood apraxia of speech: https://www.youtube.com/watch?v=sq7vFWLqodM • How to do speech therapy with toddlers at home: https://www.youtube.com/watch?v=9gTPS0cX4VQ • Autismspeaks.org • Apraxia-kids.org
	Books	• Batshaw ML, Roizen NJ, Lotrecchiano GR. (2013). *Children with Disabilities*. Baltimore, MD: Paul H. Brookes Publishing Co • Beukelman DR, Mirenda P. (2012). *Augmentative and Alternative Communication: Supporting Children and Adults with Complex Communication Needs*. 4th ed. Baltimore, MD: Paul H. Brookes Publishing Co • Coplan J. (2010). *Making Sense of Autistic Spectrum Disorders: Create the Brightest Future for Your Child with the Best Treatment Options*. New York, NY: Bantam Books

Developmental and naturalistic behavioral techniques are particularly appropriate for young children because they can be applied in everyday activities. For children with motor speech disorders, especially childhood apraxia of speech, a motor learning component is included in the therapy; the child practices carefully planned sequences of emerging sound patterns. Links to video segments demonstrating therapies for childhood apraxia of speech are listed in Table 4. Recommendations for therapy for childhood apraxia of speech include frequent but short sessions, at least 4 times per week, with family and school participation in the treatment program; preliminary evidence demonstrates promising outcomes. (57) Use of nonspeech oral motor exercises, such as blowing, lip strengthening, and lateral tongue movements, are not beneficial for the treatment of motor speech disorders primarily because speech sounds do not use the oral mechanisms in the same movements as eating or drinking. However, cues to placement of the tongue or lips for proper speech sound production may be helpful. For children with extremely limited verbal output, assistive and augmentative communication devices (AACs), such as sign language, picture exchange, or voice-activated software, may also be considered. AAC methods are often taught in schools. Unfortunately, high-technology devices may not be able to travel home with the student. In addition, family members may not learn the AAC methods and, therefore, cannot help their child to use the technique in home and community settings. To be most effective, parents and teachers should get training in the use of the AAC method and should encourage the child to use the method in all communication settings.

It may be challenging for parents and for clinicians to know whether a child is receiving high-quality speech and language therapy. In addition to the specific recommendations previously herein, high-quality therapy should include the following features:

- The speech-language pathologist establishes explicit objectives to address the areas of need in each of the domains of language or speech affected. Objectives may also be geared toward solidifying strengths in the various domains.

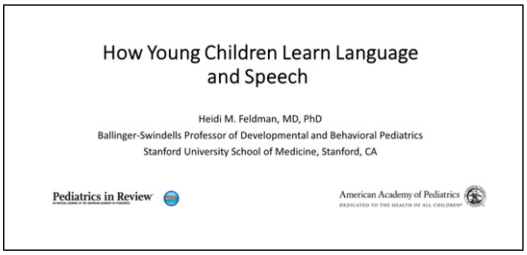
- Especially in the treatment of toddlers, preschool-age children, and young school-age children, parents are aware of the objectives and the strategies the therapist is using. Parents often follow through with exercises at home.
- Speech-language therapy at school is planned and executed in conjunction with teachers. Speech-language therapy may also be coordinated with other therapeutic services, such as occupational therapy or social skills training.
- The therapy is fun for the child. Therapy may not necessarily be conducted at a desk or table. Therapists are warm and encouraging.
- The speech-language pathologist considers strategies to ensure that improvements during the therapy session generalize to everyday environments, including home and school.
- Progress is monitored frequently and regularly. Progress reports are provided to parents, teachers, and referring clinicians.

Summary

Language is a distinctly human form of symbolic communication. Delays and disorders of language and speech are prevalent. (1) The main points of this review and the clinical implications are as follows:

- Research shows that the amount of child-directed speech is a strong contributor to the child's language development. (11)(28)(29) Based on clinical consensus in relation to these data, primary care clinicians play a role in primary prevention of language and speech disorders by counseling families about the importance of the learning environment. Reach Out and Read supports the development of language and reading.
- The US Preventive Services Task Force concluded that no studies have yet examined the effects of screening on speech and language or other functional outcomes. (58) However, based on some research and consensus, professional organizations recommend a developmental screening at age 9, 18, and 24 or 30 months and, in addition, autism screening at 18 and 24 or 30 months. (14)(15) Resources are available for parents to alert them to the early stages of delays in language and speech (Table 4).
- Research shows that male sex (19), bilingualism, (20) later birth order, (23) and otitis media (24)(25) are not causes of language delays. Therefore, children with delays and these conditions should be managed in the same manner as all other children with delays.
- Disorders of language are subdivided into receptive, expressive, and mixed receptive-expressive disorders. However, expressive difficulties may be more obvious than concomitant difficulties in comprehension. The specific diagnoses of language and speech disorders may also be predicated on the component of language or speech affected. In addition, disorders may be classified as primary when no other major disorder is present and as secondary when other conditions are present, including severe psychosocial deprivation, hearing loss, global developmental delay or intellectual disability, known genetic variants, neurologic conditions, and other health conditions, such as prematurity. Information that can be shared with parents regarding these disorders are listed in Table 4.
- Speech-language therapy has been shown to be useful for some though not all disorders of language and speech disorders. (54)(58) Nonetheless, based on this research, clinical consensus is that children with speech and/or language delay should be referred for language and/or speech therapy, either in isolation or as part of an early intervention or special education program.
- Ongoing monitoring by the primary care clinician may allow early detection of attention deficits, executive function limitations, or reading disorders, all of which may be associated with language or speech disorders. The ultimate goal of all screening, assessment, referral, and ongoing monitoring is to allow children to reach their maximal functional capacity for language and speech and to participate fully and joyfully in the human community.

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/40/8/398.supplemental.**



How Young Children Learn Language and Speech

Heidi M. Feldman, MD, PhD
Ballinger-Swindells Professor of Developmental and Behavioral Pediatrics
Stanford University School of Medicine, Stanford, CA

References for this article are at http://pedsinreview.aappublications.org/content/40/8/398.

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1. The prevention of speech and language delays is an important responsibility of pediatricians. Which of the following is the most appropriate primary prevention activity that pediatricians should focus on?
   A. Direct parents to use an adult-oriented ("mature") language approach with their children.
   B. Educate parents about encouraging language development.
   C. Emphasize the value of unstructured playtime over reading-based activities.
   D. Encourage parents to take advantage of computer-based interactions with their child.
   E. Reassure parents that language exposure intensity is only important after 18 months of age.
2. While teaching a class on early intervention for speech delay, your class asks if there is a group of children who have been identified with speech delay that will ultimately catch up and will not require speech therapy services. Of the following groups of children with identified speech delay, which group is most likely to catch up with peers without any intervention?
   A. Boys.
   B. Children from bilingual homes.
   C. Children with chronic otitis media with effusion.
   D. Later-born children.
   E. None of the above.
3. A 9-year-old boy diagnosed as having attention-deficit/hyperactivity disorder has not responded to medication treatment alone. When assessed by his local school district, he is found to have a specific language impairment. Which of the following speech features is most likely to be consistent with the results of testing in this patient?
   A. Abnormal comprehension skills.
   B. Normal phonological development.
   C. Normal short-term and working memory.
   D. Normal syntax and pragmatic language skills.
   E. Slow processing speed.
4. A 4-year-old boy is referred for further evaluation of his speech and language. The child is difficult to understand and struggles to express himself. After obtaining a speech and language therapy evaluation, the impression is that the most likely diagnosis is, in fact, childhood apraxia of speech. Which of the following speech characteristics is most likely to be consistent with this diagnosis in this patient?
   A. Abnormal pauses between sounds.
   B. Excessive use of fillers.
   C. Inconsistent errors in producing words.
   D. Repetition of individual speech sounds.
   E. Use of behavioral strategies.
5. The family of a 2-year-old child is concerned about the quality of the speech-language therapy available in their community. Although they have focused on the frequency of service, which of the following measures are most likely to be suggested by the pediatrician as a better measure of appropriate and high-quality therapy?
   A. Drill-based activities occur at every therapy session.
   B. Family receives annual progress reports.
   C. Interventions are specific to the therapy sessions.
   D. Practice occurs only during therapy sessions.
   E. Specific objectives address affected areas.

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Diabetic Ketoacidosis

Katherine Cashen, DO,* Tara Petersen, MD, MSEd†

*Division of Critical Care, Department of Pediatrics, Children's Hospital of Michigan/Wayne State University School of Medicine, Detroit, MI

†Division of Critical Care, Department of Pediatrics, Children's Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, WI

Practice Gaps

1. Clinicians should be aware of the etiology and clinical presentation of diabetic ketoacidosis.
2. Clinicians should understand the appropriate management and risks associated with treatment of children with diabetic ketoacidosis.

Objectives

After completing this article, readers should be able to:

1. Understand the etiology of diabetic ketoacidosis (DKA).
2. Understand the basic clinical presentation, diagnostic tests, and management of DKA.
3. Recognize the risks associated with fluid and electrolyte therapy in patients with DKA.
4. Understand the causes of recurrent DKA.

INTRODUCTION

Diabetic ketoacidosis (DKA) occurs when there is a relative or absolute decrease in circulating insulin levels in relation to an increase in counterregulatory hormone levels. In response to this imbalance, normal physiologic mechanisms are exaggerated, resulting in hyperglycemia, hyperosmolality, ketosis, and acidosis. (1) The biochemical criteria for the diagnosis of DKA are hyperglycemia (blood glucose level $>$200 mg/dL [$>$11.1 mmol/L]), venous pH less than 7.3 or serum bicarbonate level less than 15 mEq/L ($<$15 mmol/L), and ketonemia (blood β-hydroxybutyrate concentration $\geq$3 mmol/L) or moderate or severe ketonuria. (1)(2)(3)

Overall, the most common cause of DKA is new-onset type 1 diabetes mellitus (T1DM). DKA can also be seen in children with T1DM and infection, other intercurrent illness, or inadequate insulin administration. Children with type 2 diabetes mellitus (T2DM) may also present in DKA. High-dose corticosteroids, atypical antipsychotic agents, diazoxide, and immunosuppressive medications have been reported to precipitate DKA in patients without a diagnosis of T1DM. (4)(5)

Treatment of DKA involves careful fluid resuscitation, insulin administration, electrolyte replacement, and close monitoring for signs of cerebral edema. This review focuses on the epidemiology, pathogenesis, diagnosis, management, and

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ABBREVIATIONS

DKA	diabetic ketoacidosis
GCS	Glasgow Coma Scale
PECARN	Pediatric Emergency Care Applied Research Network
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

morbidity of DKA. We highlight diagnostic criteria, risk factors, treatment, and the risks associated with fluid and electrolyte therapy in these patients.

EPIDEMIOLOGY

Diabetes is one of the most common chronic diseases in the United States. In 2009, at least 192,000 children in the United States had a diagnosis of diabetes, and the population incidence for DKA hospitalizations continues to increase, with 188,965 total admissions in 2014. (6) Approximately 11% of these admissions for DKA were in children younger than 17 years. (7) Despite an overall increase in hospital admissions, both hospital length of stay and mortality have decreased, with mortality decreasing to 0.33%. (7)

Nearly 30% of children with a new diagnosis of T1DM present with DKA and 10% of children with a new diagnosis of T2DM present with DKA. (8)(9) Risk factors for DKA on initial diagnosis are younger age (<2 years), delayed diagnosis, and lower socioeconomic status. (2) In children with known T1DM, the risk of DKA is 1% to 10% per patient year, and risk factors for DKA include insulin omission, previous episodes of DKA, inadequate dosing of insulin, and infection. (2)(9)(10) In recurrent DKA, psychological considerations play a major role, including stress of chronic disease, rebellion against authority, fear of weight gain, and eating disorders, which have all been implicated as contributing factors. Increased risk of recurrence of DKA has also been reported in peripubertal and adolescent girls and children with challenging social situations or limited access to medical services. (2)(9)

PATHOGENESIS

DKA occurs when serum insulin concentrations are inadequate due to an absolute deficiency (as in the setting of progressive pancreatic β-cell failure due to autoimmune destruction in undiagnosed T1DM) or relative deficiency (stress, infection, inadequate insulin intake) in relation to elevated counterregulatory hormone levels (catecholamines, cortisol, glucagon, and growth hormone).

Figure 1 depicts the pathophysiology of DKA. The combination of insulin deficiency and increased counterregulatory hormone levels leads to gluconeogenesis and glycogenolysis with increased glucose production and decreased peripheral glucose utilization. This causes hyperglycemia, hyperosmolality, increased lipolysis, and ketogenesis. When the renal threshold for glucose is exceeded (~170–200 mg/dL [~9.4–11.1 mmol/L]), glucosuria and hyperketonemia cause osmotic diuresis, dehydration, and electrolyte wasting (including sodium, potassium, magnesium, calcium, and phosphate loss). (11)(12) This further stimulates stress hormone production, and if insulin, fluid, and electrolytes are not replaced, then worsening dehydration, metabolic and lactic acidosis, and even death can occur.

The pathogenesis of cerebral edema is incompletely understood. Multiple mechanisms have been suggested, and controversy exists about whether intravenous fluid administration rate and content contribute. Earlier theories suggested that rapid rehydration with hypotonic fluid and resultant fluid shifts due to a rapid decrease in osmolality between the extravascular and intravascular intracranial compartment explained the development of cerebral edema. Newer theories suggest that cerebral hypoperfusion with reperfusion injury, neuroinflammation, and vasogenic edema play a role, as does increased permeability of the blood brain barrier. A recent randomized controlled trial performed at 13 large pediatric centers, the Pediatric Emergency Care Applied Research Network (PECARN) DKA FLUID Study, compared the effects of the rate and content of intravenous fluid administration on neurologic outcomes in children with DKA. (13) In this study, only 0.9% of patients had clinically apparent brain injury, and there was no difference in neurologic outcome between the groups, suggesting that the rate of infusion is not associated with increased neurologic injury. (13) The rate of clinically apparent brain injury has remained static despite improved treatment and monitoring pathways, which suggests that the mechanism is multifactorial and that providers still have much to learn to fully understand this complex pathophysiology.

Demographic factors associated with an increased risk of cerebral edema include younger age (<5 years old), new onset of diabetes, longer duration of symptoms (often associated with severe dehydration), and severe acidosis.

CLINICAL ASPECTS

Signs and Symptoms

The classic clinical signs of DKA include polyuria, polydipsia, polyphagia, and weight loss. A good history and physical examination are necessary to prevent misdiagnosis in children who do not have classic presenting symptoms, and, even with classic signs, inexperienced providers may misdiagnose DKA. Clinical signs may progress rapidly and include vomiting, abdominal pain, dehydration, weakness, and lethargy. Abdominal pain and ileus can result from potassium depletion, acidosis, and poor splanchnic perfusion. Abdominal pain may be severe enough to mimic an acute abdomen in the initial phase of DKA. Dehydration causes tachycardia, delayed capillary refill time, poor skin

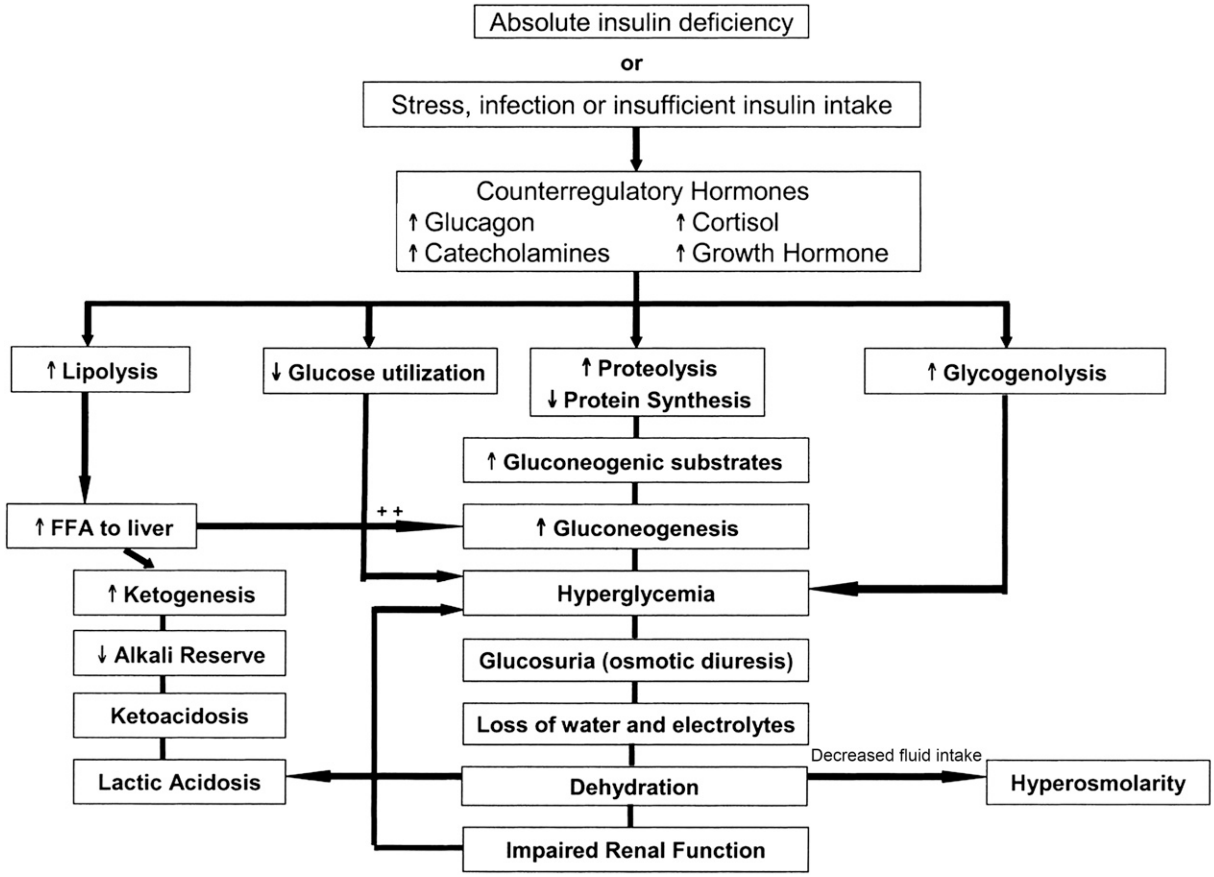


Figure 1. Pathophysiology of diabetic ketoacidosis. (Reprinted with permission from Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2018;19[suppl 27]:155–177.)

turgor, and dry mucus membranes. Ketoacidosis stimulates both central and peripheral chemoreceptors that control respiration, resulting in Kussmaul respiration (rapid fast deep breathing) in an attempt to decrease Pco_2 and compensate for the metabolic acidosis. In addition, ketoacidosis may result in a fruity odor to the breath. Despite severe dehydration, children generally maintain their blood pressure, likely due to increased plasma catecholamines and increased release of antidiuretic hormone in relation to high serum osmolality. (2) Eventually, when compensatory mechanisms are overwhelmed, children with severe DKA may present with hypotension, shock, and altered mental status.

The most feared complication of DKA is severe neurologic injury and development of cerebral edema. Warning signs and symptoms of developing brain injury include headache, bradycardia, irritability, increased drowsiness, altered mental status, cranial nerve palsies, new abnormal neurologic signs on examination, hypertension, unresponsiveness, and coma. The Glasgow Coma Scale (GCS) (Table 1) may be used to provide more objectivity when assessing mental status. (14) Recent studies have used multiple scores or a change in GCS score to assess decline in mental status in children with DKA and have shown an association between GCS score and cerebral edema on neuroimaging. (13) However, the GCS is limited because it has not been well validated as a predictor of short- or long-term outcome in pediatric DKA and, thus, should be used in conjunction with a complete neurologic examination. (13)(14)

In addition to the aforementioned history and physical examination findings, it is important to investigate potential precipitants of DKA, including, but not limited to, intercurrent infection, malfunctioning insulin pump, ingestion of medications or substances, and pregnancy.

Laboratory/Diagnostic Findings

Laboratory values necessary for diagnosing DKA are hyperglycemia (blood glucose level >200 mg/dL [>11.1 mmol/L]), venous pH less than 7.3 or serum bicarbonate level less than 15 mEq/L (<15 mmol/L), ketonemia (blood β-hydroxybutyrate concentration ≥3 mmol/L), and ketonuria. (1)(2)(3) The severity of DKA is categorized as mild (pH <7.3 or serum bicarbonate level <15 mEq/L [<15 mmol/L]), moderate (pH

TABLE 1. **Glasgow Coma Scale**

	SCORE					
	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	NA	NA
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	NA
Motor	Makes no movements	Extension to painful stimuli (decerebrate response)	Abnormal flexion to painful stimuli (decorticate response)	Flexion/withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

NA=not applicable.

$<$7.2 or serum bicarbonate level $<$10 mEq/L [$<$10 mmol/L]), or severe (pH $<$7.1 or serum bicarbonate level $<$5 mEq/L [$<$5 mmol/L]). (15)

Serum electrolytes with calculation of an increased anion gap [$Na-(Cl+HCO_3)$] greater than 12 ± 2 mEq/L is consistent with DKA. Note that this gap is attributable to the presence of serum ketones and not to other etiologies of anion gap metabolic acidosis (such as lactic acidosis, salicylates). Children will have dilutional hyponatremia due to hyperglycemia, and the calculated corrected sodium value should be considered. Corrected sodium is calculated as measured sodium + 2 ([plasma glucose − 100] / 100) mg/dL. Elevated serum osmolality, blood urea nitrogen concentration, and creatinine level are also consistent with DKA. Due to known urinary losses in the setting of glucosuria, serum calcium, phosphate, and magnesium levels are also important to monitor. In addition, an electrocardiogram should be considered in the setting of high serum potassium levels given the associated risk of ventricular arrhythmia.

A complete blood cell count with leukocytosis is commonly seen and by itself may not indicate infection. Cultures or radiographic imaging for the source of infection should be considered if the clinical history or physical examination findings are suggestive.

Findings on laboratory testing that have been associated with the development of cerebral edema are elevated serum blood urea nitrogen level, severe acidosis, and severe hypocapnia. (2) A failure of the corrected sodium level to rise with treatment, or a further decrease in serum sodium level, has been associated with cerebral edema as well. Additional laboratory tests may be warranted as the clinical examination and history findings dictate.

Timing of Initial and Subsequent Laboratory Evaluation

At the time of initial presentation, blood glucose levels, serum electrolyte levels, pH (via blood gas), and the presence of urine or blood ketones will confirm the diagnosis of

TABLE 2. **Example of 2-Bag Technique for Intravenous Replacement and Fluid Requirement**

PLASMA GLUCOSE, MG/DL (MMOL/L)	BAG 1: 0.9% NACL, PARTS	BAG 2: D_{10} + 0.9% NACL, PARTS	FINAL DEXTROSE CONCENTRATION, %
≥250 (>13.8)	1	0	0
200–249 (>11.0–13.8)	1	1	5
150–199 (>8.3–11.0)	1	3	7.5
100–149 (5.6–8.3)	0	1	10
<100 (5.6)	Assess patient	Treat hypoglycemia	

Each intravenous fluid bag should have equal electrolyte levels depending on institutional preference and protocol (eg, 30 mEq/L [30 mmol/L] of potassium acetate + 10 mEq/L [10 mmol/L] of potassium phosphate). The rate of infusion will depend on the calculated maintenance and replacement of the remaining deficit based on institutional protocol. Each child requires specific individual treatment and assessment, and adjustments to treatments should be made based on careful monitoring. D_{10}=10% dextrose, NaCl=sodium chloride.

DKA. Patients presenting in DKA with a new diagnosis of diabetes should undergo additional laboratory testing to assist with the evaluation of their underlying pathophysiology. This testing is inclusive of hemoglobin A1c, thyroperoxidase antibodies, thyrotropin, free thyroxine, tissue transglutaminases, immunoglobulin A, total immunoglobulin A, islet cell antibody, insulin antibody, and glutamic acid decarboxylase antibody.

Serial laboratory testing with hourly capillary blood glucose concentrations and frequent (every 2–4 hours) serum electrolyte, blood gas, blood urea nitrogen, calcium, magnesium, phosphate, and β-hydroxybutyrate levels should be performed. Note that capillary blood glucose levels may be inaccurate in the presence of poor peripheral circulation and severe acidosis, thereby limiting this collection method in measuring extremely high blood glucose concentrations. In these circumstances, capillary samples may need to be cross-checked against venous glucose samples. (2)

Radiologic Findings

Head computed tomography can be used to evaluate the brain parenchyma for radiologic signs of cerebral edema (Fig 2). In some cases, the radiation exposure of computed tomography may outweigh the benefit of the study. Magnetic resonance imaging may be valuable to identify cerebral edema in the setting of acute alteration in mental status for ischemic stroke, dural sinus thrombosis, and other associated neurologic injuries. Imaging is an adjunct to clinical examination findings and should not delay emergency treatment.

TREATMENT

Initial treatment of DKA should follow the guidelines of Pediatric Advanced Life Support. Management should be in a center with expertise in managing pediatric DKA. If a child needing emergency care does not present to a center with this expertise, consultation with an expert in the management of pediatric DKA is strongly recommended. Initial testing as described in the Laboratory/Diagnostic Findings subsection may be necessary, and thorough clinical examination and history are important in determining precipitating factors, estimating the severity of dehydration, and assessing mental status.

After initial life support, a child with DKA should receive care in a unit that has both experienced nurses and physicians trained in the serial monitoring and management of DKA in children and adolescents. Within this care arena, providers should follow a protocolized approach for pediatric DKA management. In addition, to provide the best and safest care, the medical team needs to have access to a laboratory that can provide frequent and timely measurements of biochemical variables. Patients with severe DKA inclusive of prolonged duration of symptoms, compromised circulation, or depressed level of consciousness should be considered for treatment in an ICU (pediatric if available) or in a unit with equivalent staffing and resources. (2)

The overall goals of treatment are to correct dehydration and acidosis and reverse ketosis, with gradual correction of hyperosmolality and hyperglycemia. Initial management includes fluid resuscitation with isotonic fluid. Note that fluid replacement should begin before starting insulin therapy. In children with hypovolemic shock (inadequate tissue perfusion from decreased intravascular volume), fluid resuscitation with isotonic saline (0.9% sodium chloride), and 20-mL/kg fluid boluses should be rapidly infused, with reassessment after each bolus. (2) In children with dehydration without shock, initial fluid resuscitation should begin with an isotonic saline fluid bolus, typically 10 mL/kg over 30 to 60 minutes. Calculation of fluid administration, including replacement from losses and maintenance fluid requirements, should be estimated over 24 to 48 hours, and 0.45% to 0.9% saline, or a balanced salt solution, may be used (Ringer's lactate, Hartmann solution, or Plasma-Lyte). (2)(13) The International Society for Pediatric and Adolescent Diabetes Consensus Statement has been recently modified to reflect that 0.45% to 0.9% saline may be used based on findings from the PECARN DKA FLUID Study. (2)(13) Patients with DKA are typically 5% to 10% dehydrated. The

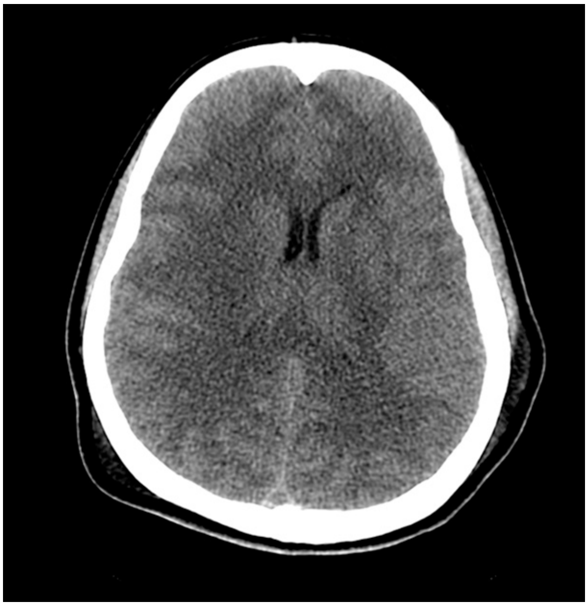


Figure 2. Computed tomographic scan showing effacement of the cerebral sulci consistent with cerebral edema.

mean time to correction of DKA was approximately 12 hours in a study of 635 patients. (16) Thus, although calculations of fluid administration should be made to replace fluid over 24 to 48 hours, most patients will correct before the 24- to 48-hour mark and will be able to restore the remaining fluid deficit via enteral replacement.

As noted previously herein, initiation of insulin therapy should follow initial fluid replacement. Initial insulin infusion rates of 0.05 to 0.1 U/kg per hour are recommended depending on the clinical scenario and degree of hyperosmolality. A continuous insulin infusion should be maintained until resolution of DKA. A small randomized controlled trial in children younger than 12 years showed that low-dose insulin (0.05 U/kg per hour) was comparable with higher dose (0.1 U/kg per hour) in terms of rate of glucose decrease and resolution of acidosis but did not suggest that higher-dose insulin was harmful. (17) The expected rate of decrease of blood glucose is 36 to 90 mg/dL per hour (2–5 mmol/L per hour). Dextrose may be added to the intravenous fluid if the rate of decrease drops faster than expected. Table 2 shows an example of the 2-bag technique for intravenous fluid replacement. If the blood glucose level falls more quickly than expected and DKA has not resolved despite the addition of up to 12.5% of dextrose peripherally, then a reduction in the insulin dose delivered should be considered. When the patient has corrected and is no longer in DKA, has improved sensorium, and is able to tolerate oral intake, he or she should be transitioned to oral food and subcutaneous insulin.

Potassium should be replaced as soon as the patient has urine output and laboratory values confirm that the child is not hyperkalemic. Despite initially normal or elevated levels of serum potassium, children with DKA typically have a total body deficit of potassium with intracellular potassium depletion due to shifts of potassium to the extracellular space and loss due to vomiting and osmotic diuresis. If children are hypokalemic on presentation, potassium should be replaced, and as long as the patient has adequate renal function, rehydration fluid should contain potassium. Depletion of intracellular phosphate is also seen in DKA due to losses from osmotic diuresis, and severe hypophosphatemia should be treated. Bicarbonate administration is not recommended because this has not shown benefit in the resolution of DKA, and bolus administration has been historically associated with worse outcomes. Administration of bicarbonate potentially may cause harm due to paradoxical central nervous system acidosis. Therefore, bicarbonate administration should be reserved for the treatment of severe hyperkalemia or severe acidosis (pH ≤6.9) causing impaired cardiac contractility. (2) Hyperchloremia may develop in children who undergo replacement with fluids containing large amounts of chloride. This can contribute to persistent hyperchloremic metabolic acidosis, large base deficit, and low serum bicarbonate level. Hyperchloremia should be considered in a child with low β-hydroxybutyrate levels with a non–anion gap metabolic acidosis and a low serum bicarbonate level.

Children with severe DKA and children at high risk for cerebral edema should be cared for in an ICU. Children who are severely obtunded or unconscious and cannot protect their airways should be intubated. In most circumstances, intubation should be avoided if possible because pharmacologic sedation and the subsequent elevation of P_{CO_2} in a child with cerebral edema may progress to cerebral herniation. Central venous catheters should be avoided due to the high risk of thrombosis in these patients. If the clinical scenario deems a central venous catheter necessary, it should be removed as soon as the patient status allows. Repeated neurologic examinations (hourly, or more frequently as clinically indicated) should be performed to assess for the development of cerebral edema (new or worsening headache, bradycardia, vomiting, change in neurologic status, new cranial nerve palsies, abnormal pupillary response, hypertension, hypoventilation). (2) Treatment of cerebral edema should be started as soon as there is clinical suspicion and should not be delayed because of neuroimaging. Hypotension, hypoxia, and excessive fluid administration should be avoided. The head of the patient's bed should be elevated to 30°, and hyperosmolar agents (mannitol or hypertonic saline [3%]) should be administered. Hypertonic saline is increasingly used in many institutions; however, controversy remains, and data are lacking to definitively dictate whether mannitol or 3% hypertonic saline is preferable in this patient population.

The mortality from DKA in children is low, and the major cause of mortality and morbidity is cerebral injury. DKA associated with central nervous system complications include neuronal changes resulting from hypoglycemia and hypoxia, dural sinus and basilar artery thrombosis, intracranial hemorrhage, cerebral infarction, and cerebral edema. Note that DKA is associated with a prothrombotic tendency in children. This is due to a combination of altered clotting factor activity and serum hyperosmolarity, which potentiate the risk of thromboembolic events, including the previously mentioned cerebral thrombosis or cerebral infarction. (18)(19)

Clinically apparent cerebral edema occurs in 0.5% to 0.9% of patients with DKA, with high mortality. Alteration in mental status (defined as a GCS score <14) occurs more commonly and has been associated with findings of cerebral edema on neuroimaging. Neuroimaging studies in children with DKA without overt clinical signs have shown that evidence of cerebral edema occurs more frequently than clinically suspected. The pathogenesis of cerebral edema is incompletely understood, and controversy exists about whether intravenous fluid administration rate and content contribute. Historically, abrupt changes in serum osmolality have been implicated in the development of cerebral edema.(20)(21) Newer theories suggest that factors intrinsic to DKA, including cerebral hypoperfusion with reperfusion injury, neuroinflammation, osmotic shifts, and vasogenic edema, play a role, as does increased permeability of the blood-brain barrier, which can worsen during treatment.(22) Meticulous monitoring of clinical and laboratory response to treatment should be provided with goals to correct rehydration, gradually improve hyperglycemia and hyperosmolality, and reverse acidosis and ketosis. A causal relationship has not been determined between the administration of hypotonic fluid or a rapid reduction in serum osmolality and the development of cerebral edema. However, caution and gradual reduction in hyperglycemia and hyperosmolality are recommended. Additional research is needed to clearly define the pathogenesis of cerebral edema and whether specific treatment interventions contribute to the development of cerebral edema.

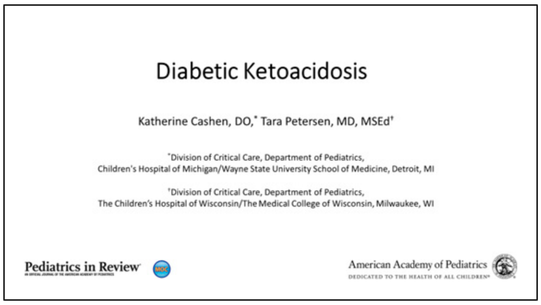
Survivors of cerebral edema after DKA have significant morbidity. Even children treated for DKA who did not have clinically apparent neurologic injury during treatment demonstrate memory deficits after recovery, suggesting that subclinical changes may contribute to morbidity. Additional reports suggest that children with altered mental status at presentation without overt clinical or radiologic findings during treatment for DKA score worse on cognitive testing, and structural and functional changes on magnetic resonance imaging persist for up to 6 months after treatment. These data suggest that measures aimed at prevention, including earlier diagnosis in patients with new-onset T1DM and improved diabetes compliance and prevention of recurrence by identifying and addressing precipitating factors, play a key role in morbidity and mortality. (2)(23)(24)

In conclusion, children with DKA should be cared for in a center with expertise in managing these ill patients. Most cases of DKA are seen in children with a new diagnosis of T1DM. Recurrent DKA is more common in children with psychosocial concerns, including difficulty with access to health care, challenging social situations, and poor compliance. Treatment goals are to correct dehydration, acidosis, and ketosis and, if possible, to avoid the development of cerebral edema. Mortality is low but morbidity, especially long-term morbidity, is not well delineated, and the underlying mechanism of neurologic injury requires additional study. Prevention via earlier diagnosis and improved diabetes compliance should be targeted.

Summary

- On the basis of class D evidence and consensus, children and adolescents with diabetic ketoacidosis (DKA) should be cared for in a center experienced in the treatment of DKA.
- On the basis of class A evidence, goals of treatment in children with DKA are to correct dehydration, correct acidosis, and reverse ketosis.
- On the basis of class A evidence, fluid replacement (deficit and maintenance) should be calculated and replaced over 24 to 48 hours.
- On the basis of class B evidence, insulin therapy should start at a rate of 0.05 to 0.1 U/kg per hour after starting fluid replacement.
- On the basis of class B evidence, bicarbonate administration is not recommended except for severe hyperkalemia or severe acidosis with impaired cardiac output.

To view teaching slides that accompany this article, visit **http://pedsinreview.aappublications.org/content/40/8/412.supplemental.**



Diabetic Ketoacidosis

Katherine Cashen, DO,* Tara Petersen, MD, MSEd†

*Division of Critical Care, Department of Pediatrics,
Children's Hospital of Michigan/Wayne State University School of Medicine, Detroit, MI

†Division of Critical Care, Department of Pediatrics,
The Children's Hospital of Wisconsin/The Medical College of Wisconsin, Milwaukee, WI

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1. A 16-year-old girl with type 1 diabetes mellitus (T1DM) is seen in the clinic for recurrent episodes of diabetic ketoacidosis (DKA). She is 5 ft 6 in (168 cm) tall and weighs 100 lb (45.4 kg). She is a well-adjusted honor roll student, and her teachers say she is a very pleasant person and gets along very well with her peers. Which of the following is most likely to be associated with her recurrent episodes of DKA?

    A. Fear of weight gain.
    B. Inadequately prescribed dosing of insulin.
    C. Low socioeconomic status.
    D. Misunderstanding insulin administration instructions.
    E. Underlying immune disorder predisposing to infection.

2. A 3-year-old girl with new-onset T1DM is admitted to the hospital with a diagnosis of DKA. On initial evaluation in the emergency department she was assessed to be severely dehydrated. Her parents report that she has been ill for a week. Laboratory studies show mild acidosis, high urine specific gravity, glucosuria, and ketonuria. Which of the following factors is least likely to place this patient at risk for cerebral edema?

    A. Age of 3 years.
    B. Mild acidosis.
    C. New onset of T1DM.
    D. Prolonged nature of her illness.
    E. Severe dehydration.

3. A 10-year-old girl with no significant medical history is brought to the emergency department because of vomiting, abdominal pain, polyuria, polydipsia, dehydration, and weight loss. She is diagnosed as having DKA. In addition to blood glucose, blood ketone, and serum electrolyte levels, which of the following laboratory studies is not recommended as part of the initial routine evaluation of this patient?

    A. Erythrocyte sedimentation rate.
    B. Glutamic acid decarboxylase antibody level.
    C. Hemoglobin A1c level.
    D. Islet cell antibody.
    E. Thyroperoxidase antibodies.

4. A 15-year-old boy, with a history of vomiting and 10% dehydration is brought to the emergency department by ambulance after his parents called 911 when they noticed that he has been progressively becoming more "lethargic" for the past few hours. On arrival at the emergency department he is noted to have clinical signs of dehydration. He is sleepy but arousable and responds to painful stimuli. His initial laboratory evaluation is significant for a blood glucose level of 250 mg/dL (13.9 mmol/L) with serum pH 7.05 and a bicarbonate level of 4 mEq/L (4 mmol/L). A normal saline bolus is started, and a computed tomographic scan of the brain is ordered. Which of the following is the most likely finding to be seen on computed tomographic scan in this patient?

    A. Brain atrophy.
    B. Dural thrombosis.
    C. Effacement of cerebral sulci consistent with cerebral edema.
    D. Intraparenchymal hemorrhage.
    E. Ischemic stroke.

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5. A 14-year-old girl with known T1DM has been noncompliant with her insulin dosing regimen. She is brought to the emergency department in DKA. Bicarbonate therapy should most likely be considered in which of the following clinical and laboratory findings?
   - A. Serum pH 7.2, potassium level of 5 mEq/L (5 mmol/L), and normal cardiac output.
   - B. Serum pH 7.0, potassium level of 6 mEq/L (6 mmol/L), and decreased cardiac output.
   - C. Serum pH 6.7, potassium level of 7 mEq/L (7 mmol/L), and decreased cardiac output.
   - D. Serum pH 7.1, potassium level of 4.5 mEq/L (4.5 mmol/L), and normal cardiac output.
   - E. Serum pH 7.0, potassium level of 6 mEq/L (6 mmol/L), and normal cardiac output.

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Index of Suspicion

1 An 11-year-old Girl with Depression and Electrolyte Disturbance

Raymen Rammy Assaf, MD, MPH, MIA,[*] Maria Levine, MD,[†]
Clement Cheung, MD, PhD,[‡] Benita Tamrazi, MD,[§] Jennifer A. Cotter, MD,[¶][**]
Michael Bryant, MD, MBA,[††] Erin N. Kiehna, MD[‡‡]

[*]Department of Pediatrics, [†]Division of Psychiatry, Department of Pediatrics, [‡]Division of Endocrinology, Department of Pediatrics, [¶]Department of Pathology and Laboratory Medicine, and [††]Division of Hospital Medicine, Department of Pediatrics, Children's Hospital Los Angeles, Los Angeles, CA
[§]Department of Radiology, [**]Department of Pathology, and [‡‡]Division of Neurosurgery, Department of Surgery, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA

EDITOR'S NOTE

On June 3, 2017, 27-year-old Alex Honnold climbed the 2,900-foot rock face of El Capitan in Yosemite National Park, alone and with neither rope nor safety net. The story is shown in the 2018 documentary film *Free Solo* and described in the 2018 book *The Impossible Climb* by Mark Synnott.

Many reading this issue of *Pediatrics in Review* have moved to new levels of responsibility this summer and might feel like they are free-soloing too.

Honnold did not do his free-solo climb on a whim. He prepared meticulously. He worked with colleagues and practiced moves for years, with ropes, on the same route that he would one day conquer on his own, unsupported. Just as with pediatric training, expertise comes with training, time, and practice.

But, what did Honnold do during the afternoon of June 3, 2017, following what the *New York Times* called "one of the great athletic feats of any kind, ever"? He worked out to strengthen his grip for future climbs. In the same way, we who care for children keep working out. We keep honing our skills. We meticulously study possible "routes" as we consider cases and differential diagnoses and management plans. After each patient care success, we keep "working out" for the next challenge.

Even so, may you use this month's *Index of Suspicion* cases to "strengthen your grip" so you can be effectively prepared to work through steep diagnostic challenges as you reach new heights of pediatric practice.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

An 11-year-old girl with a 2-year history of major depressive disorder presents to the emergency department with 10 days of anorexia, irritability, and depressed mood. She was first diagnosed as having depression 2 years ago during a 2-month-long hospitalization that mandated a psychiatric hold for physical

AUTHOR DISCLOSURE Drs Assaf, Levine, Cheung, Tamrazi, Cotter, Bryant, and Kiehna have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

aggression and suicidal ideation with concurrent anorexia requiring nasogastric feeding. Aripiprazole 1 mg daily was prescribed to target symptoms of agitation. After discharge from her first hospitalization, the patient was followed monthly by a psychiatrist and weekly by a psychotherapist, with discontinuation of pharmacotherapy 4 months later given improvement in labile mood.

Then, 11 months after that point, she was noted to clinically deteriorate, with development of severe apathy, irritability, oppositionality, and anorexia despite the absence of identifiable stressors. She was admitted again, this time for 2 weeks, for treatment of depression, oral aversion, and anorexia. Aripiprazole therapy was briefly reinitiated, but the patient was thought to have medication-induced dystonia (fist-clenching) and syndrome of inappropriate antidiuretic hormone, with a serum sodium level of 118 mEq/L (118 mmol/L). Sodium values returned to normal levels after water restriction, oral sodium supplementation, and discontinuation of aripiprazole. Concurrent diffuse headaches were evaluated with a contrast computed tomographic scan of the head, which did not demonstrate any structural abnormality or calcification. On discharge, mood and behavior were improved on fluoxetine 10 mg nightly. However, after approximately 6 weeks, the patient's depression, irritability, aggression, and oral intake worsen, and she is seen in our emergency department for these symptoms, meeting the criteria for inpatient psychiatric hospitalization.

The patient measures 51.6 in (131 cm) in height (less than the third percentile, z score $= -2$) and weighs 65 lb (29.3 kg) (eighth percentile, z score $= -1.39$), with a BMI of 18.85 (67th percentile, z score $= 0.5$), growth velocity of 1.0 in (2.5 cm) per year, and midparental height of 61.5 in (156.25 cm). Although she demonstrated a poor growth trajectory, the patient had limited follow-up with her primary pediatrician, and no previous endocrinologic evaluation had been completed. Vital signs on presentation are within normal limits, and the physical examination reveals a Tanner stage I prepubertal female (pubic hair I, breasts I) with no neurologic deficit. She is seen by a psychiatry consultant in the emergency department and is diagnosed as having major depressive disorder recurrent episode with atypical features, including increased sleep.

She is admitted to the hospital for close observation and is started on mirtazipine to target depression and poor oral intake. She develops asymptomatic hypoglycemia (glucose level of 52 mg/dL [2.9 mmol/L]) and hyponatremia (sodium level of 125 mEq/L [125 mmol/L]). Her morning cortisol level is low (<1 μg/dL [<27.6 nmol/L]), with an inappropriately normal corticotropin level (9 pg/mL [2 pmol/L]) and a subsequent failed corticotropin stimulation test, with a peak cortisol level of 2.7 μg/dL (74.5 nmol/L). Additional endocrine evaluation reveals a low free thyroxine level (0.68 ng/dL [8.75 pmol/L]), with an inappropriately normal thyrotropin level (1.41 mIU/L), a low insulinlike growth factor I level (45 ng/mL [5.9 nmol/L], −3.4 SD), and prepubertal gonadotropin and estradiol levels. Further evaluation reveals the etiology of her condition.

DISCUSSION

Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain is performed, demonstrating a cystic mass in the sella measuring 1.4 × 1.4 × 2.1 cm with suprasellar extension, displacing the optic chiasm superiorly (Fig, top row). Cyst contents are hyperintense on T1-weighted MRI and predominantly hypointense on T2-weighted MRI, with hemosiderin staining on the gradient recalled echo sequence suggestive of previous hemorrhage. Given the new findings on MRI, an underlying sellar mass supports the reason for the endocrinologic disturbances recently discovered in this patient. A differential diagnosis includes a hemorrhagic Rathke cleft cyst (RCC), predominantly cystic craniopharyngioma, hemorrhagic macroadenoma, and a germ cell tumor.

The Disorder

Central endocrinopathy is frequently associated with sellar masses, and given the patient's indolent symptoms and MRI findings, an RCC was suspected. Both RCC and adamantinomatous craniopharyngioma (ACP) originate from ectopic remnants of the Rathke pouch formed during embryonic development of the pituitary gland and have similar clinical manifestations. (1) An ACP is more likely to have calcifications on imaging, which were absent in this case. (2) On pathologic examination, an ACP typically contains squamous epithelium, whereas an RCC characteristically contains well-differentiated columnar epithelium and cilia, although the 2 conditions have been reported to coexist given their common embryologic origin. (3) In this patient, serum and cerebrospinal fluid α-fetoprotein and β–human chorionic gonadotropin test results were both negative, making germ cell tumor unlikely.

Most RCCs are asymptomatic, with the incidence ranging from 3% to 22% in adult autopsy studies. (4) Although only 10% of RCCs are found in patients younger than 16 years, these are usually symptomatic, prompting brain imaging. (5) When RCC enlargement causes acute or subacute symptoms, it commonly manifests over a period of weeks to years with headache (70%–85% of patients), visual impairment (33%), and endocrine dysfunction (66%), with diabetes insipidus, precocious puberty, and growth delay the most frequently encountered endocrinopathies. (5)

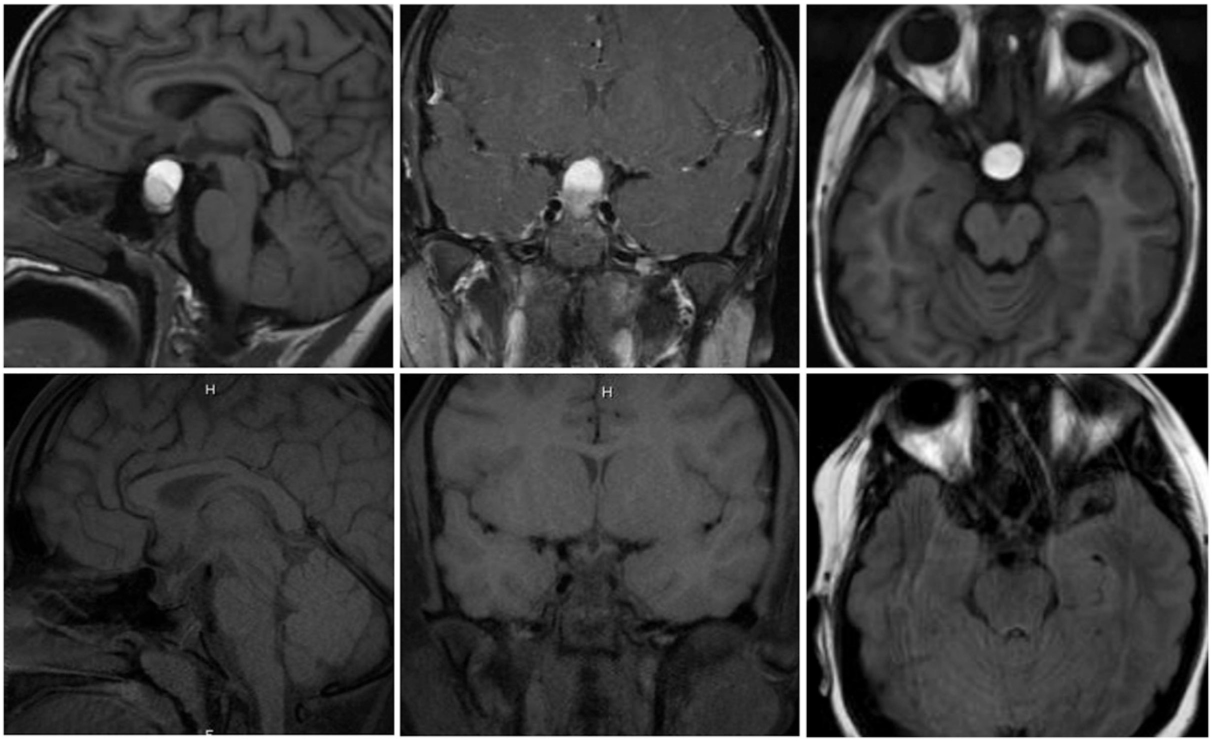

Figure. Comparison of preoperative T1-weighted magnetic resonance images (MRIs) (upper row) and MRI with dedicated images of the sella 18 months after resection via the transsphenoidal approach (bottom row). The hyperintense cystic lesion originally measured 1.4 × 1.4 × 2.1 cm, with displacement of the optic chiasm superiorly. No residual cyst is evident in the postoperative images.

Intracystic hemorrhage or inflammation secondary to cyst contents is possible and may lead to a more severe acute presentation. (5)

Diagnosis and Treatment

Clues to an underlying central endocrinopathy early in our patient's hospital admission included headache and vomiting in an 11-year-old prepubertal female patient whose height measured less than the third percentile for age, with concurrent and persistent hyponatremia (sodium level of 125–130 mEq/L (125–130 mmol/L). These findings together ultimately prompted an evaluation of a morning cortisol level and further endocrinologic evaluation, which revealed evidence of relatively low corticotropin, thyrotropin, and growth hormone levels. Bone age was found to be concordant with chronological age. An ophthalmologic examination revealed bitemporal superior quadrantanopsia and normal visual acuity, consistent with inferior chiasmal compression.

Although behavioral disturbance and executive dysfunction are well-documented consequences of hypopituitarism and in particular hypocortisolism, an association specifically between RCC and psychiatric manifestation is less described in the literature. (6) To begin with, the true incidence of pituitary cysts in childhood is not known but is thought to be uncommon, with asymptotic lesions incidentally found in 4 of 341children (1.2%) younger than 15 years in a 10-year single-center retrospective review of brain MRIs. (7) According to national mental health surveillance data for 2005 to 2011 from the Centers for Disease Control and Prevention (CDC), the prevalence of depression in children aged 3 to 17 years was reported to be 2.1%. (8) A delay in the diagnosis in our case may be attributed to the slow growth of RCC and the indolent course of additional somatic symptoms other than headache as well as limited access to primary pediatric and endocrine specialty care during the 2 years between the diagnoses of mood disorder and pituitary mass. Panhypopituitarism at the time of presentation of an RCC has been reported in up to 25% of adult patients (4) but is less frequently reported in children. (9) Note that during the 2 years before discovery of the RCC, our patient's psychiatric and somatic symptoms were not controlled with antidepressant medications.

Asymptomatic patients with incidental discovery of a small cystic lesion can be observed. (1) For patients with progressive enlargement of their lesion, endocrinopathies, or visual disturbances, surgical intervention is warranted, with pathologic slides helping differentiate RCCs and ACPs. Most sellar/suprasellar tumors are approached via the transsphenoidal route. The most common surgical strategy includes fenestration of the cyst, evacuation of cyst contents, and biopsy of the cyst wall. (1) Generally, there is minimal attempt to remove the cyst wall, and the sellar floor is left open to allow cyst drainage into the sphenoid sinus. This strategy relieves symptoms and has minimal associated pituitary dysfunction but has been associated with higher recurrence rates, approaching 30% in some series. (4) Complete resection is associated with lower recurrence rates, but there is a higher risk of pituitary dysfunction and cerebrospinal fluid leak. (1)

The patient was prescribed physiologic dosing of hydrocortisone (10 mg/m^2 per day) for secondary adrenal insufficiency, levothyroxine for central hypothyroidism, and desmopressin for central diabetes insipidus. Cyst removal was performed via the endoscopic endonasal transsphenoidal approach. On microscopic examination, intact fragments of cyst epithelium were composed of tall columnar cells with well-preserved apical cilia, a histologic finding consistent with RCC. (10) No foci of "wet keratin," stellate reticulum, or stratified squamous epithelium were present in the specimen, and, therefore, an ACP was much less likely. Repeated ophthalmologic testing with a Humphrey visual field study 3 months postoperatively reveals resolution of bitemporal superior quadrantanopsia. No residual cyst is detected on repeated MRI 5 and 18 months after neurosurgery (Fig, bottom row). Now nearly 13 years old and more than 18 months from the operative date, the patient has sustained resolution of headaches, improved energy and appetite, with normal mood and behavior off psychotropic medications. She requires ongoing replacement of hormones given central endocrinologic dysfunction and is maintained on hydrocortisone, levothyroxine, growth hormone, and desmopressin, with planned initiation of estradiol supplementation given inadequate pubertal growth secondary to hypogonadotropic hypogonadism.

Lessons for the Clinician

- Diligently following growth trajectory and Tanner staging for even subtle abnormalities may be critical in promptly diagnosing an underlying endocrinopathy, especially in the setting of unexplained electrolyte disturbance
- Only a minority of Rathke cleft cysts (RCCs) present in children; however, they are more likely to be symptomatic, in contrast to adults.
- The most common presenting symptoms of RCC include headache, visual disturbances, and endocrine dysfunction.
- Craniopharyngiomas manifest similarly to RCCs, and although each has characteristic radiologic findings, histopathologic analysis is needed to distinguish one from the other.
- Evacuation of cyst contents is the most common surgical approach, and cysts rarely recur. Complete cyst resection carries a higher risk of pituitary dysfunction and cerebrospinal fluid leak.

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Case 1: An 11-year-old Girl with Depression and Electrolyte Disturbance

Raymen Rammy Assaf, Maria Levine, Clement Cheung, Benita Tamrazi, Jennifer A. Cotter, Michael Bryant and Erin N. Kiehna

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Case 1: An 11-year-old Girl with Depression and Electrolyte Disturbance

Raymen Rammy Assaf, Maria Levine, Clement Cheung, Benita Tamrazi, Jennifer A. Cotter, Michael Bryant and Erin N. Kiehna

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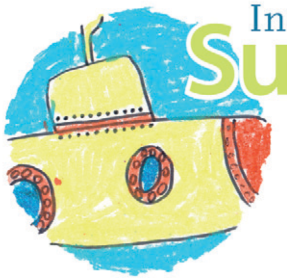

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2 A 4-year-old Boy with Recurrent Vomiting

Seema Jain, MD,*[†] Lefkothea P. Karaviti, MD, PhD*[†]

*Baylor College of Medicine, Houston, TX
[†]Texas Children's Hospital, Houston, TX

PRESENTATION

A 4-year-old boy presents with recurrent episodes of vomiting over a 2-month period. The vomit is nonbloody, nonbilious, and not associated with diarrhea or fever. There seems to be no specific pattern to the vomiting, although the patient's father suspects that it is the result of eating too many potato chips. Accompanying symptoms include a 2-lb (907-g) weight loss, fatigue, and darkening of eczematous lesions. His medical history includes eczema, constipation, and hospitalization at age 6 weeks for vomiting, failure to thrive, hyponatremia, and hyperkalemia, which were attributed to a urinary tract infection and improper formula mixing. The evaluation at that time showed normal renal ultrasonography and voiding cystourethrography findings. His family history reveals a 26-year-old male maternal first cousin who presented with similar symptoms as a young child and is now being treated with testosterone for delayed puberty. In addition, 4 maternal uncles passed away during infancy because of reported infections and high fever. A maternal aunt passed away at 2 years of age from an unknown cause. The patient is mildly tachycardic (heart rate, 102 beats/min) and normotensive (blood pressure, 91/57 mm Hg). His temperature is 97°F (36.1°C), and respirations are 18 breaths/min. Physical examination shows hyperpigmented macules over the right antecubital fossa, left gluteal region, perioral region, and gums; the remainder of the examination findings are normal. Laboratory studies show hyponatremia (sodium level of 124 mEq/L [124 mmol/L]), hypochloremia (chloride level of 94 mEq/L [94 mmol/L]), and metabolic acidosis (carbon dioxide level of 17 mEq/L [17 mmol/L]). Glucose, potassium, and calcium levels are normal. His cortisol level at 8 AM is low (6.7 μg/dL [184.9 nmol/L]), and his corticotropin level is significantly elevated (2,368 pg/mL [521 pmol/L]; reference range, 9–57 pg/mL [2–12.5 pmol/L]), as is the plasma renin level (48,600 pg/mL [1,151.8 pmol/L]; reference range, 250–5820 pg/mL [5.9–137.9 pmol/L]). Additional testing reveals the diagnosis.

DISCUSSION

A corticotropin stimulation test shows cortisol levels of 3.4, 3.5, and 3.4 μg/dL (93.8, 96.6, and 93.8 nmol/L) at 0, 30, and 60 minutes, respectively. Peak cortisol levels less than 18 μg/dL (<496.6 nmol/L) 30 and 60 minutes after the administration of cosyntropin are consistent with a diagnosis of adrenal insufficiency. (1) The initial clinical presentation, along with corticotropin level, can

AUTHOR DISCLOSURE Drs Jain and Karaviti have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

help providers differentiate between primary (adrenal cortical disease) and secondary (pituitary disease) adrenal insufficiency. Primary disease causes a low cortisol level with a subsequent elevation of corticotropin because of feedback mechanisms, and secondary disease causes a low corticotropin level, which results in a low cortisol level. Our patient has a low cortisol level, an elevated corticotropin level, and evidence of salt wasting and hyperpigmentation on examination, all consistent with primary adrenal insufficiency. To evaluate the etiology of primary adrenal insufficiency, 17-hydroxyprogesterone, 21-hydroxylase antibody, and very long-chain fatty acid analysis are performed, and the results are within the reference range. Given the family history, which is suggestive of an X-linked disease (Fig), genetic testing is performed for the *NR0B1* gene. The result reveals a pathogenic variant of the *NR0B1* gene, which is diagnostic for X-linked congenital adrenal hypoplasia. (2) The patient receives intravenous fluid replacement and is started on "stress-dose" hydrocortisone (100 mg/m^2 per day). With clinical improvement, hydrocortisone is decreased to "triple dose" (30 mg/m^2 per day), and fludrocortisone (0.1 mg twice a day) is started. Once back at his baseline status, the patient is sent home on maintenance hydrocortisone (10 mg/m^2 per day) and fludrocortisone, and the family is taught sick-day management for adrenal insufficiency. With appropriate treatment, follow-up laboratory test results show normalization of electrolyte, corticotropin, and plasma renin levels, and hyperpigmentation improves significantly. He is currently thriving as a healthy child with normal weight and linear growth that is within his genetic potential.

The Condition

Congenital adrenal hypoplasia, also known as adrenal hypoplasia congenital, is a rare condition with a reported incidence of 1 in 12,500 births. (2) Most affected individuals present in the first few months of life with failure to thrive, hyponatremia, hypoglycemia, and hyperpigmentation. Early diagnosis and treatment are imperative and can prevent sudden death. (3) Older individuals may present with a preference for salty foods (eg, potato chips) and with concomitant illness that precipitates adrenal failure. Hypogonadotropic hypogonadism is commonly associated with congenital adrenal hypoplasia, and patients can present with cryptorchidism, delayed or arrested puberty, and infertility. (2) Congenital adrenal hypoplasia results from mutations in the *NR0B1* gene, which encodes DAX1 on chromosome Xp21. (2)(4)(5) Of note, deletions in Xp21 can cause a contiguous gene syndrome with congenital adrenal hypoplasia that involves glycerol kinase deficiency and Duchenne muscular dystrophy. (6) As seen in our patient, a positive family history consistent with X-linked inheritance is likely to reveal a pathogenic variant in *NR0B1* in almost 100% of affected individuals. (2) Genetic counseling that addresses carrier status and recurrence risks should be provided.

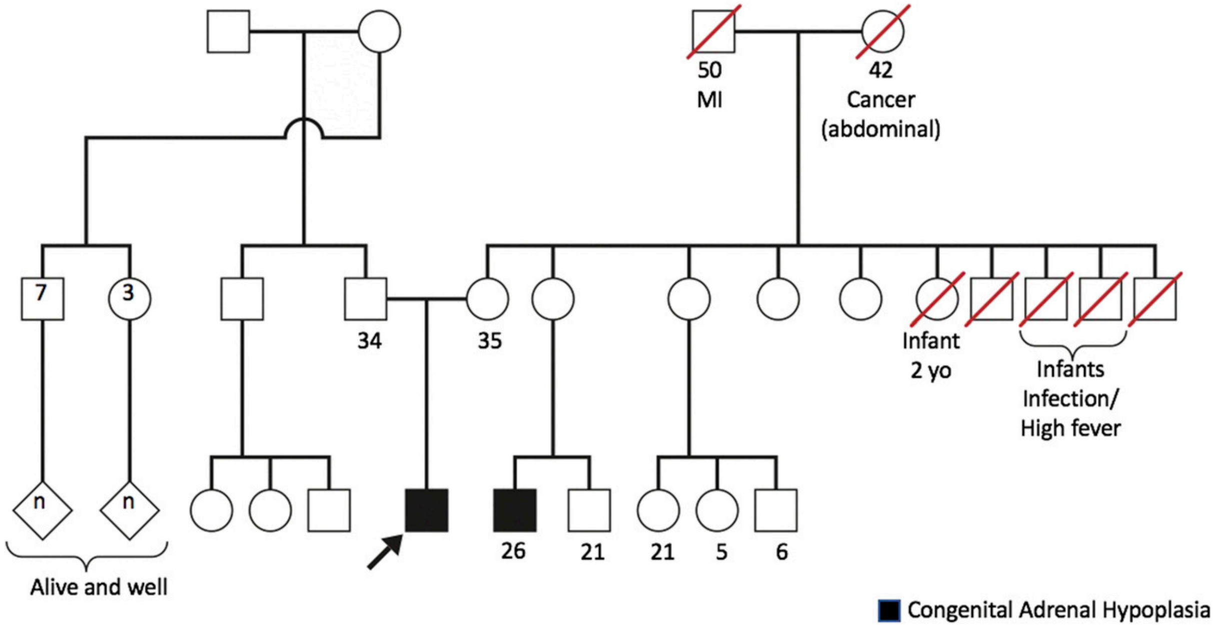

Figure. Pedigree reveals the proband (black arrow) and a male maternal first cousin with congenital adrenal hypoplasia. Four maternal uncles passed away during infancy due to reported infections and high fever. A maternal aunt passed away at 2 years of age from an unknown cause.

Differential Diagnosis

When the diagnosis of adrenal insufficiency is established, the underlying etiology, whether primary or secondary, should be sought. Both primary and secondary adrenal insufficiency can present with symptoms of glucocorticoid deficiency, which include fatigue, nausea, vomiting, fasting hypoglycemia, and decreased free water clearance, which can cause mild hyponatremia. However, only primary adrenal insufficiency will present with mineralocorticoid deficiency (hyponatremia, hyperkalemia, metabolic acidosis) and hyperpigmentation (due to a stimulant effect of elevated corticotropin levels). Important endocrine causes of primary adrenal insufficiency include congenital adrenal hypoplasia (*NR0B1* mutation), congenital adrenal hyperplasia (elevated 17-hydroxyprogesterone level), Addison disease (a positive 21-hydroxylase antibody test result), adrenoleukodystrophy (high levels of very long-chain fatty acids), and autoimmune polyglandular syndrome (*AIRE-1* gene mutation). Of note, nonendocrine causes of primary adrenal insufficiency include infections (tuberculosis, human immunodeficiency virus, cytomegalovirus) and medications (ketoconazole, etomidate). Common causes of secondary adrenal insufficiency include hypopituitarism, central nervous system malformations, tumors, irradiation, trauma, and withdrawal from glucocorticoid therapy. (5)

Management

Acute management of an adrenal crisis includes fluid and salt replacement with isotonic, dextrose-containing fluids and initiation of stress-dose hydrocortisone. Patients should receive a single bolus of intramuscular or intravenous hydrocortisone 100 mg/m^2, followed by 100 mg/m^2 per day. Once patients improve clinically, they can be weaned down to triple-dose hydrocortisone (30 mg/m^2 per day) and started on fludrocortisone (0.05–0.2 mg daily). Stress-dose hydrocortisone has adequate mineralocorticoid activity; however, triple-dose hydrocortisone does not, so fludrocortisone therapy should be initiated. Long-term maintenance therapy once the patient is back at baseline status consists of hydrocortisone (8–10 mg/m^2 per day) and fludrocortisone. Of note, longer-acting glucocorticoids (dexamethasone, prednisone) can be used for maintenance therapy in adults; however, they are rarely used in children because of concerns of cushingoid adverse effects and reduced final height. (1)(5)(7) Adherence and disease activity are monitored by growth velocity, skin hyperpigmentation, and electrolyte, corticotropin, and renin levels. Secondary adrenal insufficiency can be solely treated with hydrocortisone because mineralocorticoid activity remains intact, and these patients, thus, do not require fludrocortisone supplementation.

Lessons for the Clinician

- Infants presenting with vomiting, hyponatremia, and failure to thrive should raise high clinical suspicion for primary adrenal insufficiency, particularly in the context of multiple medical visits.
- Differential diagnosis of primary adrenal insufficiency includes congenital adrenal hypoplasia, congenital adrenal hyperplasia, Addison disease, adrenoleukodystrophy, autoimmune polyglandular syndrome, infections, and medications.
- Hyperpigmentation is often seen in primary but not secondary adrenal insufficiency and is the result of the stimulant effect of elevated corticotropin levels in melanocytes because corticotropin is part of the melanocortin molecule.
- Early diagnosis and treatment with fluid replacement and stress-dose hydrocortisone are imperative.
- Hypogonadotropic hypogonadism is commonly associated with congenital adrenal hypoplasia and results from mutations in the *NRB01* gene. (4) Patients can present with cryptorchidism, delayed or arrested puberty, and infertility. (2)
- A positive family history consistent with X-linked inheritance is likely to reveal a pathogenic variant in *NR0B1* in almost 100% of affected individuals. (2)

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Case 2: A 4-year-old Boy with Recurrent Vomiting

Seema Jain and Lefkothea P. Karaviti

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Case 2: A 4-year-old Boy with Recurrent Vomiting

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3 Left Eye Swelling in a 9-year-old Girl

Ashlie Tseng, MD,* Madhu Gowda, MD,† Clifton Lee, MD*

*Division of Pediatric Hospital Medicine and
†Division of Hematology, Oncology, and Stem Cell Transplantation, Department of Pediatrics,
Children's Hospital of Richmond at Virginia Commonwealth University School of Medicine, Richmond, VA

PRESENTATION

A 9-year-old girl presents to the emergency department for left eye proptosis and headaches. The symptoms started approximately 2 months earlier, and initially the parents decided to watch when the symptoms first developed as there was a strong family history of hyperthyroidism and proptosis. When the symptoms persisted for a month, she was brought to an optometrist, who noted conjunctival injection on examination, and was given antihistamine ophthalmic drops for a concern of allergies. The symptoms did not improve, however, and she saw her pediatrician and was subsequently sent to the emergency department for evaluation.

Initial complete blood cell count, basic metabolic panel, liver function tests, and thyroid function tests are normal. A computed tomographic (CT) scan of the head is performed and demonstrates a 4.0 × 5.5 × 4.0-cm retro-orbital enhancing mass. The patient is then transferred to a tertiary academic medical center for further evaluation and care. On admission, her vital signs consist of a temperature of 99.1°F (37.3°C), heart rate of 86 beats/min, respiratory rate of 22 breaths/min, and blood pressure of 117/58 mm Hg. On physical examination, her pupils are equal, round, and reactive to light, with intact extraocular movements and normal conjunctiva. She has left eye proptosis. An ophthalmologic evaluation is performed that shows that intraocular pressures are normal at 14 mm Hg on the right and 15 mm Hg on the left, and visual acuity is 20/20 on both sides, with sharp borders of the optic disc. Also notable is mild swelling anterior to her left ear toward her jaw that is painful on examination. Physical examination findings are otherwise normal. Further evaluation yields the diagnosis.

DISCUSSION

Patient Course

With the finding of the retro-orbital mass on the orbital CT scans, further CT scans of the neck, chest, abdomen, and pelvis were obtained and did not show any evidence of metastatic disease. Magnetic resonance imaging (MRI) of the head/orbit confirmed the mass, 5.5 × 4.5 × 4.1 cm, centered in the left sphenoid bone without orbital or intracranial involvement but extending into the infratemporal fossa with probable involvement of temporalis muscle, as well as superior rectus and left lateral rectus muscles (Fig). Open biopsy was performed by neurosurgery,

AUTHOR DISCLOSURE Drs Tseng, Gowda, and Lee have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

and initial pathologic testing yielded a preliminary diagnosis of sarcoma. After that diagnosis, a lumbar puncture evaluation and bilateral bone marrow aspiration and biopsy were performed, and neither test showed evidence of malignancy. A bone scan showed localized uptake in the left orbital ridge/temporal bone. Histopathologic analysis revealed that the specimen consisted of a monomorphic population of round to spindle-shaped cells with hyperchromatic nuclei arranged in a vague pattern of alternating cellularity. Several mitoses are noted on hematoxylin and eosin stain; however, no areas of necrosis or definitive skeletal muscle differentiation were noted in the lesional tissue. Immunohistochemical stains showed positivity for desmin and MyoD1 and were negative for myogenin. Due to the atypical nature of the appearance of the cells, the sample was sent for a second opinion and was confirmed as rhabdomyosarcoma favoring the spindle cell/sclerosing variant.

The patient was diagnosed as having retro-orbital parameningeal rhabdomyosarcoma stage 3, clinical group 3, making it an intermediate-risk disease. Although rhabdomyosarcoma confined to the orbits has a better prognosis, the tumor passing into the infratemporal fossa through the calvarium made it a parameningeal tumor with intermediate-risk categorization. She was started on chemotherapy with vincristine, dactinomycin, and cyclophosphamide and was referred for radiotherapy to start at week 4. Owing to the proximity to the brain, proton beam therapy was considered more appropriate to reduce the risk of long-term adverse effects of cranial radiation, and she was referred to a proton beam therapy center for the same. Owing to the minimal response that she had had with the first cycle of therapy and the atypical appearance of the tumor on independent pathology review, the diagnosis was questioned and she underwent gross resection of the tumor, and the diagnosis was again confirmed to be rhabdomyosarcoma. As she recovered from surgery, she received proton beam radiation to 41.4 Gy, boosted to 50.4 Gy to the positive margins. She completed the remainder of her chemotherapy and was in remission for approximately 3 months when she had recurrent disease, which was not responsive to salvage with doxorubicin/ifosfamide or vinorelbine/cytoxan/temsirolimus. She had 30 Gy of whole brain radiotherapy for leptomeningeal disease and eventually died.

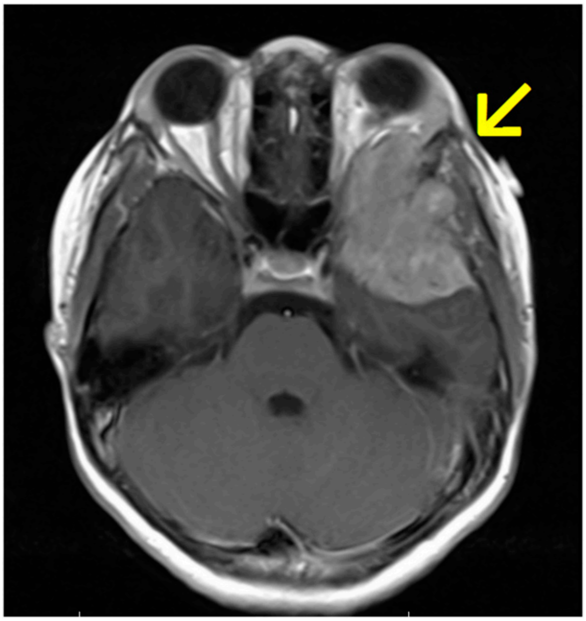

Figure. Magnetic resonance image demonstrating a soft tissue mass (yellow arrow) centered in the left sphenoid bone.

Differential Diagnosis

Proptosis or exophthalmos is the forward projection or displacement of the eyeball. Although exophthalmic measurements in children are based on age, the maximum asymmetry noted in the normal distribution of pediatric patients is 2 mm. (1) As such, it has been suggested that in the pediatric population, unlike adults, a lower limit than 2 mm for asymmetry should be used to prompt further evaluation. (1)

The differential diagnosis of unilateral proptosis is broad and may include trauma or infectious/inflammatory etiologies such as Graves ophthalmopathy or orbital cellulitis. (2)(3)(4) It is important to note that thyroid ophthalmopathy can present with unilateral or bilateral proptosis. (5) Other causes to consider include primary versus secondary neoplasms such as rhabdomyosarcoma, retinoblastoma, metastatic neuroblastoma, retinoblastoma, leukemia, lymphoma, optic glioma, Langerhans cell histiocytosis, dermoid cyst, or even hemangioma. Although most space-occupying orbital lesions in children are benign, malignancy remains a concern, especially in the case of additional systemic symptoms, such as fever. Rhabdomyosarcoma and other primary malignant tumors of the orbit compose a large portion of orbital malignancies in the United States, whereas in other countries secondary neoplasms are more prevalent. (2)(3)(4) As such, a wide differential should always be considered in a patient who presents with exophthalmos, especially because the findings can be subtle and affect timing of patients to seek medical care. This patient started developing symptoms 2 months before presentation, and earlier diagnosis possibly could have affected prognosis and management.

Diagnosis and Treatment

As in this case, retro-orbital rhabdomyosarcomas typically present, compared with other space-occupying lesions, with a rapid onset and progression of proptosis and globe displacement. (6) Patients with orbital rhabdomyosarcoma largely present without metastatic disease. (7) Symptom manifestations depend on the origin and location of the lesion. Prognosis is generally favorable, but factors are related to age, site of origin, tumor size, resectability, presence of metastases, number of metastatic sites and tissues, staging, histopathologic subtype, and localized therapy with surgery or radiation. (8) Staging for rhabdomyosarcoma is based on pretreatment location, size, nodal involvement, and evidence of metastases, whereas grouping is based on initial surgical procedure or procedures before medical therapies and also considers lymph node involvement. (9) Both staging and grouping are used for risk stratification and to guide therapies. The treatment for orbital/parameningeal rhabdomyosarcomas is chemotherapy, often routinely including radiotherapy and surgery. (6)

Lessons for the Clinician

- The differential diagnosis for proptosis is varied; however, providers should consider neoplasm or malignancy and use the history and physical examination to guide management.
- Orbital rhabdomyosarcoma is rapid in onset and progression, and symptom manifestation depends on the location of the lesion.
- Treatment of orbital rhabdomyosarcoma involves a combination of chemotherapy, radiotherapy, and surgery.
- Many factors, including age, site, resectability, presence of metastases, histopathology subtype, and localized treatment, affect a generally favorable prognosis.

NOTE. This case is based on a presentation by Drs Tseng, Stevens, Gowda, and Lee at Pediatric Hospital Medicine 2014, Clinical Conundrum, Lake Buena Vista, FL, Poster Session: A, Presentation Date: July 25, 2014, Poster Number: 15.

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Case 3: Left Eye Swelling in a 9-year-old Girl

Ashlie Tseng, Madhu Gowda and Clifton Lee

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4 An Infant with Status Epilepticus and Stroke

Firdhous Alimathunisa Abdul Kather, MD,* Kallol Kumar Set, MD*

*Division of Pediatric Neurology, Children's Hospital of Michigan, Detroit, MI

PRESENTATION

A 33-day-old boy is admitted to the hospital with seizure episodes. The antenatal course was complicated by gestational diabetes mellitus and group B streptococcus (GBS) urinary tract infection for which the mother received intrapartum antibiotic drug therapy. The patient was born at term by induced vaginal delivery because of prolonged rupture of membrane but with Apgar scores of 8, 9, and 9 at 1, 5, and 10 minutes, respectively, without any birth asphyxia, meconium aspiration, and nuchal cord. On the day of admission, the patient started having tonic-clonic movement involving the left upper extremity associated with left arm extension, fisting of the left hand with squeezing movement, and eye deviation to the left associated with grunting. He continues to have seizures until he is given 4 doses of intravenous lorazepam 0.1 mg/kg, a loading dose of levetiracetam 20 mg/kg intravenously, and phenobarbital 20 mg/kg intravenously. He also presents with fever (rectal temperature of 102.9°F [39.4°C]), which is treated with 10 mg/kg of rectal acetaminophen twice.

On examination, peripheral capillary refill is 3 seconds. He has no spontaneous eye opening but is responding to painful stimuli. The anterior fontanelle is bulging, and pupils are 2 mm and reacting normally. Funduscopic examination did not show retinal hemorrhage, but optic disc margins were not clear bilaterally. Movement is diminished overall, but no movement of the left upper and lower extremities is present. The Moro reflex is incomplete, but rooting and sucking reflexes are present. Four beats of ankle clonus are present bilaterally. Initial laboratory evaluation demonstrates a C-reactive protein level of 1.57 mg/L (14.9 nmol/L) (reference range, <9.10 mg/L [<86.7 nmol/L]), a calcium level of 8.4 mg/dL (2.1 mmol/L), capillary blood pH 7.35 with P_{CO_2} of 38 mm Hg, and a lactate level of 18 mg/dL (2 mmol/L). A complete blood cell count reveals a total white blood cell count of 2,100/μL (2.1×10^9/L), with 33% lymphocytes and 49% neutrophils, and Gram-positive cocci are found in the blood.

DISCUSSION

The cerebrospinal fluid (CSF) findings showed a red blood cell count of 24/μL (0.000024×10^{12}/L), a white blood cell count of 66/μL (0.066×10^9/L) (neutrophils 93%, monocytes 1%), a glucose level of 17 mg/dL (0.94 mmol/L), a protein level of 0.22 g/dL (2.2 g/L), and gram-positive cocci, suggestive of bacterial meningitis.

AUTHOR DISCLOSURE Drs Abdul Kather and Set have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Set's current affiliation is Division of Pediatric Neurology, Dayton Children's Hospital, Dayton, OH.

Clinical Course and Management

The patient was started on broad spectrum antibiotic drug therapy because there were concerns for meningitis. Head ultrasonography showed bilateral subdural effusions consistent with bacterial meningitis. An electroencephalogram showed diffuse neuronal dysfunction and focal seizures from the right central parietal region.

Magnetic resonance imaging (MRI) performed on day 2 showed a right posterior frontal anterior parietal acute infarct involving the precentral and postcentral gyrus (Fig 1). Also, there was multifocal loculated diffusion restriction, likely a collection of pus or small subdural empyema around the frontal and parietal convexity more on the right side, fitting the clinical presentation (Fig 2). Contrast-enhanced MRI of the brain showed leptomeningeal enhancement consistent with meningitis (Fig 3). There were no visible retinal hemorrhages found in gradient echo MRI; therefore, suspicion of child abuse was low, but it was included in the differential diagnosis initially. Also, a dilated eye examination did not show retinal hemorrhage.

The patient had a prolonged episode of seizure progressing to status epilepticus. He was started on a midazolam drip (continued for 5 days) with an increased dose of levetiracetam (60 mg/kg per day) and phenobarbital (5 mg/kg per day). The culture returned positive for *Streptococcus agalactiae* sensitive to ampicillin. A central venous catheter was placed, and ampicillin therapy was continued. Clinically, the patient stopped having seizures, and the weakness of the left upper extremity improved. MRI, electroencephalography, and lumbar puncture were repeated on day 29 (Figs 1–3).

On day 29, MRI showed cystic encephalomalacic changes in the right parietal lobe with the resolution of extra-axial diffusion restriction and substantial improvement of leptomeningeal enhancement (Fig 3). CSF continued to show 26 nucleated cells, 59% neutrophils. CSF culture showed no growth. After 33 days of ampicillin therapy, the central line was removed and the patient was discharged on oral levetiracetam and phenobarbital.

Final Diagnosis

The infant was diagnosed as having severe late-onset bacterial GBS meningitis with acute stroke, subdural empyema, and status epilepticus.

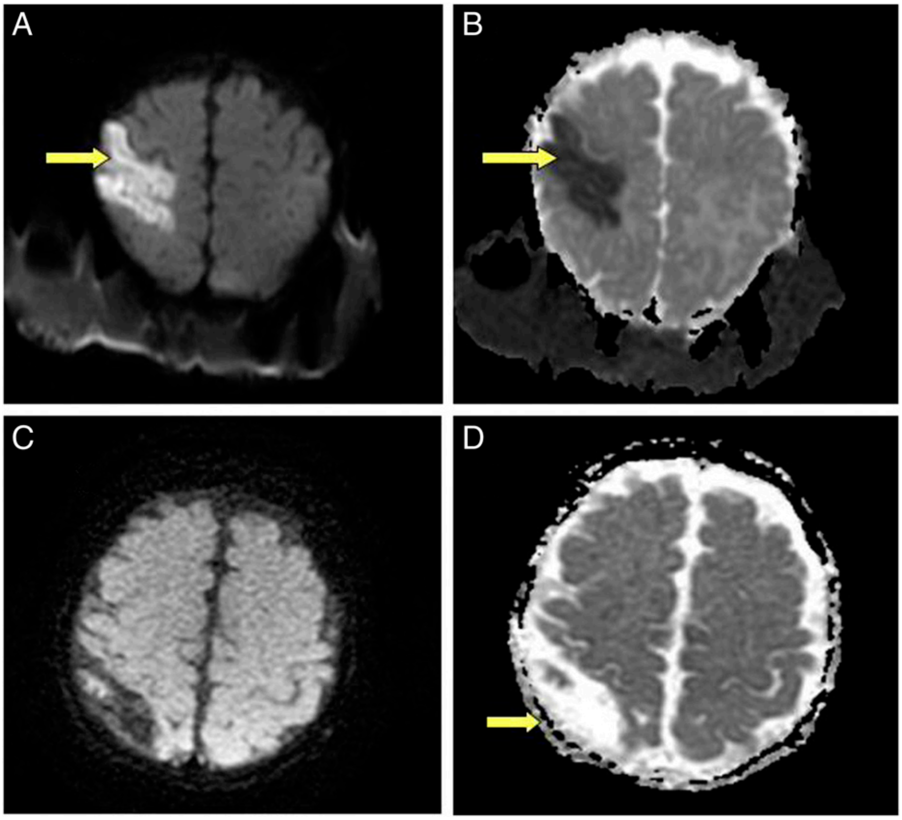

Figure 1. Magnetic resonance imaging of the brain. A and B. Diffusion-weighted image and apparent diffusion coefficient image demonstrate a focal, parenchymal, somewhat wedge-shaped diffusion restriction (yellow arrows) along the right precentral and postcentral gyrus. C and D. There is no diffusion restriction after treatment, but encephalomalacic changes (yellow arrow) are noted.

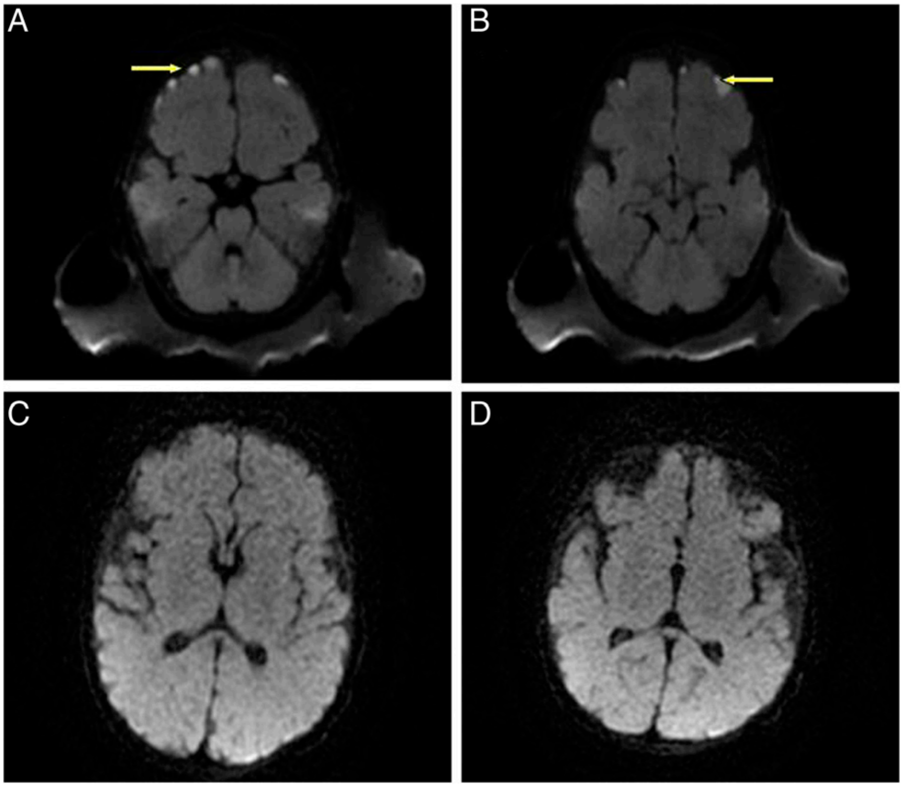

Figure 2. Magnetic resonance imaging of the brain. A and B. Multifocal small diffusion restriction (yellow arrows) along the frontal and parietal convexity is more prompt on the right side, raising the possibility of subdural empyema. C and D. The restriction disappeared after treatment.

The Condition

Bacterial meningitis is a pia-arachnoid infection and an inflammatory response in the CSF. It is a common manifestation of late-onset (day 7–89 after birth) neonatal sepsis. It occurs in 25% of neonates with bacteremia, with an incidence ranging from 0.25 to 1 per 1,000 live births. In developed countries, bacterial meningitis is commonly caused by GBS serotype III, accounting for 50% to 78% of all cases. Late-onset infections suggest nosocomial or community acquisition, or perinatal transmission from human milk, although the maternal flora colonizing the neonate may still be a source of infection.

Universal screening of pregnant women in the United States for rectovaginal GBS colonization at 35 to 37 weeks' gestation and administration of intrapartum antimicrobial prophylaxis to carriers has reduced the incidence of early-onset

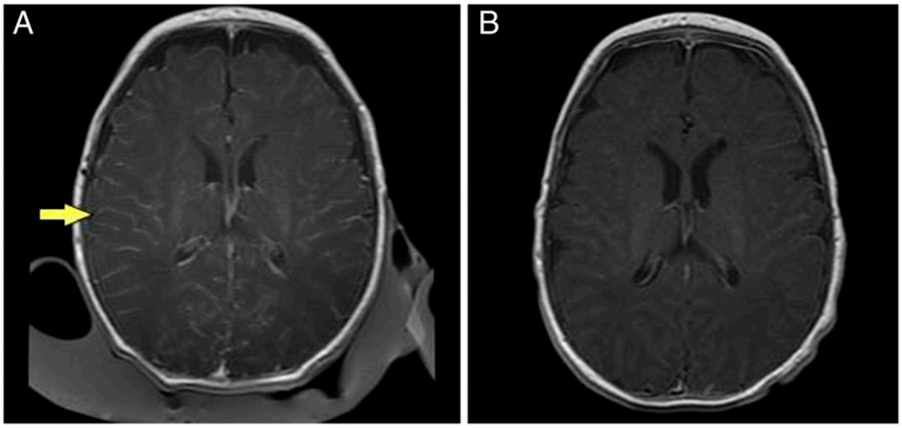

Figure 3. Magnetic resonance imaging of the brain. A. Leptomeningeal enhancement (yellow arrow) is seen after gadolinium administration. B. Enhancement disappears after treatment.

disease, but the incidence of late-onset disease has remained stable at an average of 0.34 per 1,000 live births in the United States.

GBS infection presents with symptoms such as fever (81%), irritability/crying (42%), and poor feeding (39%). Twenty percent to 50% of infants with meningitis present with seizures. Up to 50% of infants with a history of meningitis will be neurologically impaired, and 25% will have a severe disability. Meningitis is a very rare cause (∼3%) of arterial ischemic stroke in children. Hernández et al showed that the penetrating lenticulostriate and thalamostriate arteries, which supply the basal ganglia, thalamus, and deep white matter, are mostly affected (88%), and superficial cortical infarction was observed in 75% of patients.

Common neurologic complications of meningitis include ventriculitis (20%), cerebral edema and increased intracranial pressure (78%), seizures (17%–40%), cerebral infarction (30%–50%), subdural effusion or empyema (7%–33%), hydrocephalus (24%), hearing loss (7%–12%), intellectual disability (4%), and developmental delay (25%).The uncommon neurologic complications of meningitis are spinal cord ischemia, brain abscesses, aneurysm formation of focal intracranial vessels, and cortical visual loss.

Eight percent to 33% of infants with bacterial meningitis have accumulation of extra-axial fluid or subdural collection of pus. This may, in turn, become an empyema, which is present in up to 1% of affected patients. If not treated early and properly, this may require surgical drainage.

Empirical therapy of possible neonatal meningitis should include intravenous ampicillin (300 mg/kg per day) or cefotaxime plus gentamicin (4–5 mg/kg per day). Once GBS have been identified and the susceptibility verified, penicillin G (450,000–500,000 U/kg per day) can be used to complete therapy for a minimum of 14 days and should be extended to 21 days or longer if complicated. Seizures are controlled with first-line antiepileptic drugs such as lorazepam, diazepam, phenobarbital, phenytoin (older babies), and levetiracetam for 1 week up to 12 months after the last seizure, and patients should regularly follow up with a neurologist.

Lessons for the Clinician

- Despite recent advances in neonatal intensive care, rapid diagnosis, and treatment, neonatal bacterial meningitis is one of the most common causes of neurologic disability.
- Despite prophylactic intrapartum antibiotic drug therapy, late-onset group B streptococcus infections in infants continue to occur and are associated with higher morbidity than are early-onset infections.
- High clinical suspicion, early diagnosis, immediate institution of therapy, and early recognition and management of complications can decrease the mortality rate and result in a better neurologic outcome.
- Subdural effusions could have been from shaking, and the stress of abuse can lead to group B streptococcus infection. Severe shaking can also cause a brain infarct and fever. So, a dilated retinal examination, magnetic resonance imaging of the eye with gradient-recalled echo sequence, or a skeletal survey is needed to exclude child abuse/inflicted brain injury.

Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/40/8/431.

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Case 4: An Infant with Status Epilepticus and Stroke

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in Brief

Osteochondrodysplasia

Amy Liu, MD, MPH,* Jennifer McEntee, MD, MPH†
*Department of Pediatrics and †Department of Pediatrics and Internal Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

INTRODUCTION

Osteochondrodysplasias (skeletal dysplasias) are composed of more than 450 disorders that result in skeletal abnormalities due to mutations in genes that are vital to skeletal maturation and growth. Each specific type of skeletal dysplasia is very rare, with achondrodysplasia being the most common with a prevalence of 1 in 25,000 births. The collective incidence of these disorders is estimated to be 1 per 4,000 births, although some studies suggest that this may underestimate the true incidence.

These disorders have historically been categorized into 3 broad subtypes: osteodysplasias, chondrodysplasias, and dystoses. Frequently, the classification of various subtypes of skeletal dysplasias is challenging due to the genetic variance of these disorders, which may involve abnormalities in cartilage and bone development. With improvements in molecular testing, more than 350 genes have been identified, with *COL2A* and *FGFR* as the most commonly identified genetic loci involved in skeletal dysplasias. Given the heterogeneity of these conditions, The International Skeletal Dysplasia Society in 2015 revised the conditions to 42 groups defined by various molecular, biochemical, and radiographic criteria.

Throughout this *In Brief*, the presentation of various types of osteochondrodysplasias will be discussed, including their clinical manifestations, what to consider while eliciting the medical and family history, various diagnostic features, and tips on how to provide the best care to these patients.

CLINICAL PRESENTATION AND EVALUATION

Individuals with skeletal dysplasias typically present with disproportionate short stature, where the skeletal growth differs between the limbs and the trunk, as opposed to the proportionate short stature that is more commonly seen in patients with abnormal growth secondary to endocrine, nutritional, or other genetic disorders. Obtaining upper/lower segment ratio and arm span measurements in a patient with short stature is helpful in further identifying disproportion. Careful observation of the upper limbs in a patient can provide clues to disproportionate shortening if the arms do not reach the mid-pelvis during infancy or the upper thigh after infancy. If limb shortening is noted, the particular segment of the limbs (ie, proximal versus middle versus distal) that is affected may provide additional clues for certain diagnoses. In many individuals with skeletal dysplasias, length or height will be below the third percentile, although some dysplasias will demonstrate less height discrepancy.

Age at onset is a key feature in identifying a specific type of skeletal dysplasia. Almost one-third of patients with skeletal disorders have onset of short stature in the prenatal period. Therefore, an accurate evaluation of weight, length, and head

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circumference at birth can be extremely helpful in infancy. These measurements can also aid in the evaluation as they will allow a foundation for metrics in individuals who present at a later age with concerns about short stature.

In addition to abnormal growth parameters, craniofacial findings such as frontal bossing, flat nasal bridge, midface hypoplasia, and cleft palate are common in certain dysplasias. Orthopedic abnormalities, including frequent joint dislocations, scoliosis, or even the location of orthopedic joint abnormalities, provide important information that may further elucidate the diagnosis. Other nonorthopedic manifestations of skeletal dysplasias can occur, including

TABLE. Signs and Symptoms Frequently Seen in Specific Skeletal Dysplasias

ASSOCIATED SIGNS AND SYMPTOMS	SPECIFIC SKELETAL DYSPLASIA
Cervical instability	Metatropic dysplasia, SED congenital, pseudoachondrodysplasia, chondrodysplasia punctata
Chronic kidney disease	Jeune syndrome
Coccygeal tail	Metatropic dysplasia
Congenital heart malformations	Ellis–van Creveld syndrome, Jeune syndrome, chondroectodermal dysplasia
Degenerative joint disease	Diatrophic dysplasia, SED tarda, pseudoachondroplasia, multiple epiphyseal dysplasia, diaphyseal aclasia, cleidocranial dysplasia
Double-layered patella	Multiple epiphyseal dysplasia
“Hitchhiker” thumbs and “cauliflower ears”	Diastrophic dysplasia
Immunodeficiency	Cartilage-hair hypoplasia, Schimke dysplasia, McKusick metaphyseal chondrodysplasia
Joint dislocations	Larsen syndrome
Lethal (usually fatal)	Metatropic dysplasia, rhizomelic chondrodysplasia punctata, campomelic dysplasia, thanatophoric dysplasia, achondrogenesis, short rib–polydactyl syndrome, osteogenesis imperfecta type II, homozygous achondrodysplasia
Neonatal stippling of epiphyses	Chondrodysplasia punctata
Retinal detachment	Spondyloepiphyseal dysplasia, Kneist dysplasia
Sex reversal[a]	Campomelic dysplasia
Spine involvement	SED congenital, SED tarda, Kneist dysplasia, metatropic dysplasia, diastrophic dsyplasia, spondyloepimetaphyseal dysplasia, Morquio syndrome
Ventriculomegaly, foramen magnum stenosis	Achondrodysplasia
Windswept knees[b]	Pseudoachondroplasia

SED=spondyloepiphyseal dysplasia.

[a] *46XY, but have female features.*

[b] *Windswept knees consist of a valgus deformity in 1 knee with a varus deformity in the opposite knee.*

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neurologic, pulmonary, cardiac, renal, ophthalmic, and auditory complications. The Table summarizes common signs and symptoms associated with certain types of dysplasias.

Family history of other affected individuals, parental consanguinity, and fetal losses or stillbirths are all important to consider because genetic inheritance may be autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive in many disorders. Despite the genetic cause of most skeletal dysplasias, many cases are due to new mutations with no known family history.

DIAGNOSTIC APPROACH

A complete radiographic evaluation is likely the single most helpful tool in diagnosing skeletal dysplasias. Many radiologists recommend a skeletal survey followed by a radiologic algorithm, including a full set of skeletal radiographs of the skull, entire spine, pelvis and hips, chest, long bones of extremities, hands, and feet depending on radiologic findings. The timing of when in the life span of the child the imaging is obtained can be very important. In general, imaging should be conducted as soon as a skeletal dysplasia or growth deformity is suspected, with serial imaging following initial radiographs. For patients presenting after childhood, obtaining previous radiographs may be helpful because many radiographic abnormalities can change with time and often a diagnosis cannot be made at an early age. Radiographic images before closure of growth plates (age 12–14 years in females and 14–16 years in males) are most helpful because clear images of epiphyseal anatomy before fusion to the metaphysis are often necessary during the diagnostic stage.

Disproportionate physical examination findings with confirmatory radiographic findings associated with detailed medical, family, and genetic history can help pediatricians in identifying certain clinical phenotypes of specific skeletal dysplasias. These diagnoses are often complex, and a multidisciplinary approach with the assistance of geneticists and radiologists is optimal. For patients with suspected or confirmed skeletal dysplasia, genetic testing should be ordered to confirm the diagnosis and counsel families regarding future reproductive decisions. Although histologic sampling of the epiphyses is not necessary for many diagnoses, it can help further identify chondrodysplasias due to distinct histologic growth patterns.

TREATMENT

Once the correct diagnosis has been made, ongoing medical care should be provided by an interdisciplinary team that often includes the primary care provider, geneticist, genetic counselor, radiologist, orthopedic surgeon, physical therapist, occupational therapist, social worker, and home health nurse. This team will need to work together to continually assess the medical, psychosocial, and emotional needs of these patients and their families. There is no current definitive or curative treatment for these disorders; therefore, the goal in managing these dysplasias is to treat the nonskeletal manifestations of their disease, prevent further skeletal collapse, and correct skeletal deformities that could potentiate issues going forward.

Routine vision and hearing examinations are recommended because certain skeletal dysplasias are associated with myopia, glaucoma, and hearing impairment. Recurrent ear infections can contribute to hearing loss, and consultation with an otolaryngologist for tympanostomy tubes may be useful. Due to jaw malformation or malocclusion, it is highly recommended for these patients to be under routine dental care. Occupational therapy can also work with families to modify home and work environments to support an individual's independence given that simple things such as personal hygiene can be very difficult with shortened limbs.

Cervical spine abnormalities, including C1-C2 instability and odontoid hypoplasia, are increasingly recognized as complications in these skeletal disorders. Frequent surveillance for signs of subluxation or spinal cord compression along with routine cervical extension-flexion films is important because many patients may require additional surgical management. Patients can also present with significant genu varum or valgum that results in hip, knee, and ankle pain, which may require osteotomies. Degenerative joint disease is common in many of these disorders, for which hip and knee replacement may be necessary in adulthood.

As children age and mature into adulthood, it is extremely important to have a smooth transition from pediatric to adult care providers at the appropriate time for each patient. Pediatricians can help to facilitate this transition by directly discussing the individual's medical needs with the future adult provider.

COMMENT: Due to the ability to do more accurate genetic testing, the myriad of osteochondrodysplasia diagnoses are being found to be due to specific genetic mutations.

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Although for many there may be obvious physical findings, having the accuracy of genetic testing is helpful for precision of diagnosis, for better understanding of the pathophysiology and long-term manifestations of the disease, and for genetic counseling. Primary care providers will benefit from consulting with radiologists and geneticists in making the diagnosis and in counseling patients and families. Patients, families, and providers alike may benefit from advocacy groups such as Little People of America, which can provide not only medical information, psychosocial support, and understanding of some of the challenges but also useful strategies for everyday life.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

Correction

An error appeared in the print version of the June 2019 *In Brief* "Achondroplasia" (Pereira E. *Pediatr Rev.* 2019;40(6): 316-318; doi: 10.1542/pir.2018-0009). The second sentence of the second paragraph should read: "Some studies have seen a distinctive 'collar hoop' sign wherein there is a small bony protuberance at the interface between the femoral metaphysis and the diaphysis." The online version of the article has been corrected, and a correction notice has been posted with the online version of the article. The journal regrets the error.

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Osteochondrodysplasia

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Immunoglobulin A Nephropathy

Smita Goodman, DO,* Jessica Reid-Adam, MD*
**Icahn School of Medicine at Mount Sinai, New York, NY*

Immunoglobulin A nephropathy (IgAN) is the most common form of primary chronic glomerular disease worldwide. First described in 1968 by pathologist Jean Berger, it was regarded for many years as a benign condition. However, the widespread use of kidney biopsy has provided better insight into its full consequences, demonstrating it to be an important chronic, slowly progressive cause of end-stage renal disease in the pediatric population, leading eventually to renal failure in many patients. An immune complex–mediated nephropathy, IgAN is defined immunohistologically by the presence of glomerular IgA deposition accompanied by a mesangial proliferative glomerulonephritis.

IgAN is most common in white and Asian populations, with a peak incidence in the second and third decades of life. The annual incidence in the United States is reported to be 0.5 pediatric cases per 100,000. In Japan, remarkably, the incidence is 10 times as high, but worldwide the highest incidence of IgAN is in Southeast Asia. This is thought to result at least in part from increased screening for urinary abnormalities and a lower threshold for renal biopsy in patients with asymptomatic microscopic hematuria, leading to increased diagnosis. The 2:1 male/female predominance in North America and Western Europe is not seen in Asian populations. Although the true prevalence of IgAN remains unknown, its prevalence has been inferred from the proportion of cases identified in large series of kidney biopsies.

The current understanding of IgAN's pathogenesis, referred to as the *multi-hit hypothesis,* is that the disease arises as a consequence of multiple sequential pathogenic "hits." IgA, the most abundant antibody in humans, exists in 2 isoforms, IgA1 and IgA2, present in secretions and on mucosal surfaces to protect against mucosal pathogens. IgA1 is distinguished by a hinge region that carries a variable complement of O-linked carbohydrates. The key pathogenic driver of IgAN is the polymeric IgA1 form found in its mesangial IgA deposits; in fact, changes in the composition of these O-glycan chains are the most consistent finding worldwide in patients with IgAN, with identical changes in multiple cohorts. The synthesis of poorly galactosylated IgA1 O-glycoforms and their subsequent release into the circulation leads to the formation of high-molecular-weight immune complexes that are prone to mesangial deposition. The series of distinct pathogenic "hits" in the multi-hit hypothesis thus begins with aberrantly O-galactosylated IgA1 glycoforms, leading to the production of antibodies specifically targeting O-glycan chains and then to the formation of IgA1-containing immune complexes. The deposition of these immune complexes in the glomerular mesangium results in cellular proliferation, release of proinflammatory and profibrotic mediators, and overproduction of extracellular matrix, cytokines, and chemokines. This myriad array of insults ultimately leads to glomerular injury.

AUTHOR DISCLOSURE Drs Goodman and Reid-Adam have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Increasing genetic evidence suggests that heritable factors influence the risk of IgAN across ethnically diverse populations and affect the pathogenesis of IgAN. The composition of circulating IgA O-glycoforms, particularly the serum level of galactose-deficient IgA1, has been identified as a heritable trait in several ethnic groups. High levels of serum galactose-deficient IgA1 are seen in first-degree unaffected relatives of patients with IgAN; however, the absence of clinical renal disease supports the belief that other contributing factors are necessary for disease expression. Genome-wide association studies have identified loci associated with polymorphisms in the major histocompatibility complex and pathways involving both mucosal immunity and complement activation, suggesting other potential pathogenic pathways leading to IgAN.

The diagnosis of IgAN requires a kidney biopsy. Findings on light microscopy may be minimal and often vary among patients. The most common appearance is mesangial hypercellularity, which is often diffuse and global; other glomerular lesions may include focal necrosis, segmental scarring, and cellular crescents in the Bowman space. Immunohistologic analysis shows the predominance of diffuse and global IgA deposits in the mesangium. Although complement component C3 is frequently detected on immunohistologic analysis, serum C3 levels are usually normal. Electron microscopy demonstrates mesangial and paramesangial electron-dense deposits corresponding to IgA immune complexes; occasionally, deposits are also apparent in the glomerular capillary wall, in either the subepithelial or subendothelial space.

The similarity between IgAN and Henoch-Schönlein purpura (HSP), the most common form of systemic vasculitis in children, is especially notable. Many factors suggest that the 2 conditions share a common pathogenic pathway. Both diseases share pathology findings on biopsy of mesangial IgA deposition, as well as changes in the serum IgA1 O-glycoforms. Although some experts consider HSP to be part of a spectrum of disease with IgAN, the kidney disease that accompanies HSP is often self-limited, and a minority of patients have persistent renal manifestations.

The Oxford classification of IgAN (2016) is an international scoring system that uses histologic features on the diagnostic biopsy to stratify risk and prognosis. The presence of the following 5 components correlates most strongly with clinical outcome: mesangial hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, crescent scores, and endocapillary hypercellularity. These factors are cumulative, with the presence of each adding to the risk of progressive kidney disease.

Episodic gross hematuria is the presenting complaint in most children and adolescents. Hematuria often follows a characteristic time course, appearing within 24 hours of the onset of an upper respiratory or gastrointestinal illness. Visible hematuria resolves spontaneously over several days, although microscopic hematuria may persist between episodes. The time to the onset of gross hematuria differentiates IgAN from poststreptococcal or postinfectious glomerulonephritis, where the hematuria is usually not evident until at least 2 weeks after the initiating illness. Evidence of proteinuria in the nephrotic range is uncommon at presentation and is principally seen in patients with advanced glomerulosclerosis or with features of minimal-change disease on kidney biopsy. Acute kidney injury is uncommon but may develop secondary to severe immune and inflammatory injury, resulting in crescent formation. Alternatively, acute kidney injury may occur with glomerular hematuria, leading to tubular occlusion by red blood cell casts and glomerular injury. Adults may present with hypertension, proteinuria, or microscopic hematuria, alone or in combination.

Despite advances in our understanding of the pathogenic mechanisms underlying this common glomerulonephritis, no disease-targeted treatment is available for IgAN. Rather, management remains limited to generic strategies applied to all chronic glomerulonephritides, with treatment targeted at preserving renal function. Patients presenting with mild disease as evidenced by normal blood pressure, normal renal function, and low-grade proteinuria do not require treatment. However, patients with IgAN and chronic kidney disease (CKD) stages 1 to 3 should have at least annual assessments of renal function, blood pressure monitoring, and quantification of proteinuria to detect progressive disease. Renin-angiotensin blockade with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker should be introduced in patients with persistent proteinuria to slow progression of CKD and limit proteinuria. Intensive immunosuppressive agents (glucocorticoids with cyclophosphamide or azathioprine) are recommended for patients with rapid deterioration in renal function or heavy persistent proteinuria.

The course of IgAN is variable. Patients who enter a sustained clinical remission or have only persistent low-grade hematuria or proteinuria can have a relatively benign course. Others may have stage 3 or 4 CKD at the time of biopsy and progress to end-stage renal disease in childhood or adolescence. Slow progression of CKD occurs in up to 40% of patients across 30 to 40 years, leading eventually to end-stage renal disease in adulthood. Although the clinical outcome is variable, severe glomerular pathological features, impaired renal function, sustained hypertension, and substantial proteinuria independently predict poor renal prognosis.

Transplant is the treatment of choice for patients requiring renal replacement therapy. After kidney transplant, recurrent deposition of IgA in the allograft is common, with as many as 50% of grafts affected within 5 years. Although recurrence is common, failure of the graft from recurrent IgAN is much less frequent, seen most often in patients who had a rapidly progressive course in their native kidneys. As with primary disease, no specific treatment is available for recurrent IgAN after a kidney transplant.

Further advances are needed to develop diagnostic markers and novel therapeutic agents targeted specifically to this important cause of kidney failure in children and adults.

COMMENT: Most of us nonnephrologists are more familiar with HSP than with the isolated kidney disease of IgAN. Although it is true that children with HSP are at risk for a nephropathy marked by mesangial IgA deposits, the sine qua non for this systemic IgA-mediated vasculitis is its purpuric rash, not renal involvement. When the rash is present, the diagnosis is fairly straightforward, although in the absence of other typical findings the differential diagnosis is substantial: meningococcemia and other invasive bacterial infections; Rocky Mountain spotted fever; a variety of viral infections; Kawasaki disease; and thrombocytopenias. Those other typical findings that solidify the diagnosis include abdominal pain, often accompanied by evidence of gastrointestinal bleeding and occasionally intussusception; arthralgias or frank arthritis; and urinary abnormalities, such as hematuria or proteinuria reflecting underlying renal pathology. The diagnosis of HSP is sometimes obscured when the gastrointestinal or joint findings precede the rash; only when the purpura emerges does that eureka moment arrive.

– Henry M. Adam, MD
Associate Editor, *In Brief*

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Tickborne Diseases in Children in the United States: 1. D; 2. B; 3. E; 4. D; 5. D.
How Young Children Learn Language and Speech: 1. B; 2. E; 3. E; 4. C; 5. E.
Diabetic Ketoacidosis: 1. A; 2. B; 3. A; 4. C; 5. C.

Immunoglobulin A Nephropathy

Smita Goodman and Jessica Reid-Adam

Pediatrics in Review 2019;40;439
DOI: 10.1542/pir.2018-0119

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SIDS, BRUE, and Safe Sleep Guidelines

Maria Behnam-Terneus, DO,*† Melissa Clemente, MD*

*Division of Pediatric Hospital Medicine and †Medical Education Department, Nicklaus Children's Hospital/Nicklaus Children's Health System, Miami, FL

Practice Gaps

In 2016, the American Academy of Pediatrics (AAP) published a clinical practice guideline in which they recommended redefining apparent life-threatening event with the more specific term brief resolved unexplained event (BRUE). The purpose of this review is to detail how to apply the BRUE classification guidelines in practice. The recently updated AAP guidelines for sudden infant death syndrome prevention and safe infant sleeping environment are also discussed.

Objectives

After completing this article the reader should be able to:

1. Distinguish and explain the defining characteristics and epidemiology of sudden unexpected infant death, sudden infant death syndrome (SIDS), brief resolved unexplained event (BRUE), and apparent life-threatening event.
2. Apply the new BRUE guidelines and risk stratification to determine lower-risk versus higher-risk patients.
3. Review management recommendations for lower-risk BRUE.
4. Delineate risk factors and prevention recommendations for SIDS.
5. Explain the updated American Academy of Pediatrics recommendations for a safe infant sleeping environment.

INTRODUCTION

In April 2016, the American Academy of Pediatrics (AAP) published a new clinical practice guideline for brief resolved unexplained events (BRUEs). This new term, risk classification, and management recommendations replaced what was formerly known as an apparent life-threatening event (ALTE). BRUE describes transient events without a clear etiology after a thorough medical evaluation by a clinician, in contrast to ALTE, in which the definition refers to the subjective experience of a frightening event by a caregiver is detailed. In addition, the new guideline recommendations differentiate a BRUE from episodes that might warrant further investigation secondary to an increased risk of a serious underlying condition.

The purpose of this review is to clarify the differences between these 2 definitions, as well as to distinguish them from sudden infant death syndrome

AUTHOR DISCLOSURE Drs Behnam-Terneus and Clemente have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
ALTE	apparent life-threatening event
BRUE	brief resolved unexplained event
CPSC	Consumer Product Safety Commission
SIDS	sudden infant death syndrome
SUID	sudden unexpected infant death

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(SIDS) and sudden unexpected infant death (SUID). Historically, ALTE was thought to be linked to SIDS; however, evidence reveals striking differences between these 2 conditions, which continues to reaffirm that they are not interconnected. Current known risk factors and preventive strategies for SIDS and SUID are also discussed.

DEFINITIONS

Sudden Unexpected Infant Death

Also known as sudden unexpected death in infancy, SUID is an inclusive term used to characterize any sudden and unexpected death, whether explained or unexplained, occurring during the first year of life and does not have an obvious cause before further investigation. (1)

Sudden Infant Death Syndrome

SIDS is defined as a sudden, unexpected death before 12 months of age that occurs in a previously healthy infant, in which the cause of death remains unknown despite a thorough case investigation, including a complete autopsy, death scene investigation, and analysis of the clinical history. (1) SIDS is a subcategory of SUID and composes approximately half of these cases; other common causes of SUID events are strangulation and accidental suffocation. This is illustrated in Fig 1.

Apparent Life-Threatening Event

ALTE is a term coined by the National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring in 1986 and is defined as “an event that is frightening to the observer and that is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually limpness), and choking or gagging.” (2) This was created to discard the old definition that would categorize these episodes as “near missed SIDS,” enabling clinicians and researchers to separate ALTE from SIDS as 2 different entities. However, due to its broad description, ALTE introduced ambiguity as well as difficulties in application to patient care and further research. One of the challenges is basing the definition on a subjective description by an inexperienced or medically naive caregiver, who is often distraught and unable to recall the event accurately. Although concerning to the caregiver, these episodes are not often life threatening, and frequently may be either a self-limited condition or a benign phenomenon of normal infancy (eg, periodic breathing). The ALTE concept is also very broad and imprecise and includes an extensive differential diagnosis. In a minority of patients, the event may be an undiagnosed severe disease process that may result in

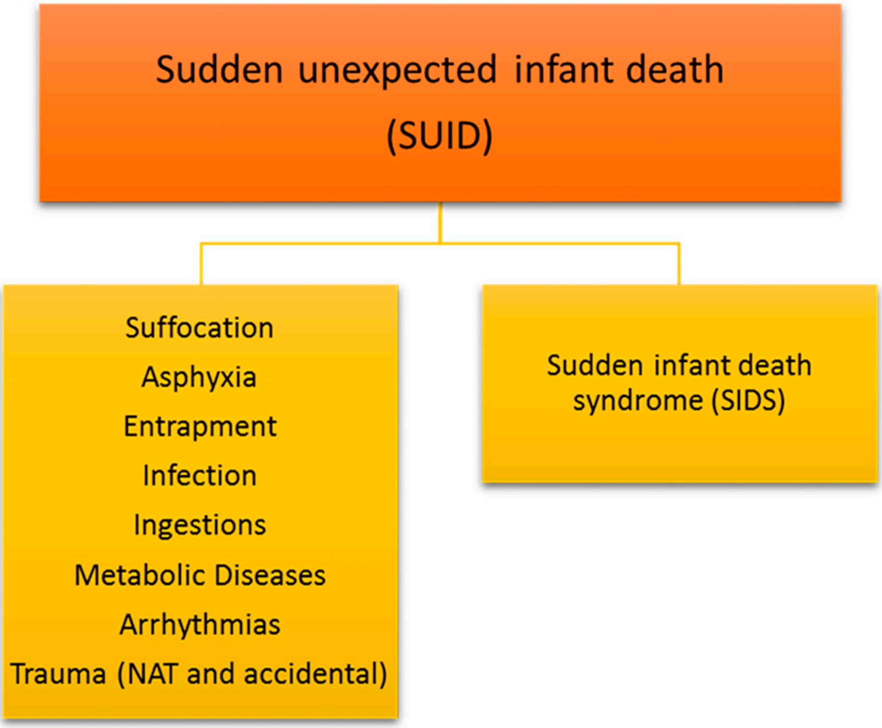
Sudden unexpected infant death (SUID)
Suffocation
Asphyxia
Entrapment
Infection
Ingestions
Metabolic Diseases
Arrhythmias
Trauma (NAT and accidental)
Sudden infant death syndrome (SIDS)

Figure 1. Sudden unexpected infant death (SUID) classification. NAT=nonaccidental trauma.

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significant illness and mortality. This small possibility can drive clinicians to do extensive, unnecessary evaluation in all infants presenting with ALTE, as well as recommend admission to the hospital for monitoring. This, in turn with inpatient evaluation, can result in escalated parental anxiety and increased risks for the infant inherent to a hospitalization, which will frequently not lead to a final diagnosis or a management plan to help prevent recurrent events. (1)

Brief Resolved Unexplained Event

A BRUE is defined as "an event occurring in infants younger than 12 months of age that is described by the observer as brief (lasting less than 1 minute, but typically <20-30 seconds), resolved (meaning the patient returned to baseline state of health after the event), and with a reassuring history, physical examination, and vital signs at the time of clinical evaluation by trained medical providers." During a BRUE, "the observer reports ≥1 of the following: cyanosis or pallor; absent, decreased or irregular breathing; marked change in tone (hypertonia or hypotonia) and altered level of responsiveness." (3) The authors reinforce the idea that to diagnose a BRUE there cannot be any other explanation for the event. For example, events in which the history and physical examination findings are compatible with a choking episode, seizures, or gastroesophageal reflux are by definition not considered BRUEs. Differences between BRUEs and ALTEs are further depicted in Table 1.

EPIDEMIOLOGY

Sudden Infant Death Syndrome

In the United States, approximately 2,300 infants die of SIDS each year. Although its incidence has declined since the 1994 "Back to Sleep" campaign, SIDS continues to be the second leading cause of postneonatal death and the fourth most common cause of death in infancy. (6) In the past 20 years, there have been increases in other causes of SUIDs. This is thought to be primarily due to advances and augmented training in death scene investigation, and as a result, deaths once classified as SIDS are now often more accurately diagnosed (eg, child abuse and sleep-related asphyxia). Consequently, the percentage of SUID events due to accidental/mechanical suffocation and strangulation in bed has increased significantly over time, from 2.1% in the neonatal population and 3.4% in the postneonatal population in 1999 to 22.7% and 24.9%, respectively, in 2014. (7)

Apparent Life-Threatening Event/Brief Resolved Unexplained Event

Accurate ALTE epidemiology is difficult to obtain based on the imprecise nature of the definition, the lack of an *International Classification of Diseases* code for ALTE until 2012, and the possibility of an ALTE eventually having an etiologic explanation. In the latter case, the diagnosis of ALTE might then be substituted with a separate final diagnosis. The estimated incidence varies between 0.6 and 5.0 per 1,000 live births and accounts for 0.6% to 1.7% of all emergency hospital visits in patients younger than 1 year. (8)

A recent meta-analysis was published regarding the risk of death in patients with BRUE. Owing to the lack of studies using this terminology, most of the studies included were related to ALTE. The mortality estimate was 1.8 postevent deaths per 10,000 patient-months of follow-up, which can be translated into a risk of death of approximately 1 in 800. For comparison, the overall risk of death of an infant in the

TABLE 1. **BRUE versus ALTE Characteristics (3)(4)(5)**

CHARACTERISTIC	BRUE	ALTE
Infant age	<1 y	Not specified
Event is characterized by	Clinician	Caregiver
Color change	Episodic pallor or cyanosis	Any color change (including plethora)
Breathing	Any breathing irregularities: absent, diminished, or any other irregularities	Apnea
Tone	Marked change in tone	Any change in tone
Choking or gagging, or any other explanation	Excluded	Included
Responsiveness	Altered level of responsiveness	Not mentioned

ALTE=apparent life-threatening event, BRUE=brief resolved unexplained event.

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general population over a similar period is estimated to be 1 in 500. Because this is extracted from the ALTE population, without distinction of a lower or higher risk of BRUE, it can be presumed that the mortality risk for patients with lower risk of BRUE is probably even less. (9)

To date, there are no reports of the incidence of BRUE because this terminology has been recently introduced, but further study of this condition might improve our understanding of this phenomenon.

The Relationship Between ALTE/BRUE and SIDS. There is no evidence that having an ALTE is a predisposing factor for SIDS. The 2 entities have some distinct epidemiologic differences, as outlined in Table 2. There are more differences than similarities between the 2 conditions. (11) The only risk factor that has been shown to influence both entities is maternal smoking, which is known to be implicated in many other health conditions, yet there is not enough evidence to link maternal smoking to the etiology of ALTE and SIDS. Research into the relationship between ALTE and SIDS has determined that only 4% to 13% of patients with SIDS had a history of apnea, a number only mildly increased compared with controls. (4)

BRUE EVALUATION AND DIAGNOSIS

As detailed previously, BRUE describes a witnessed episode occurring in a child younger than 1 year, lasting less than 1 minute, after which the patient returns to his or her baseline health status, including normal appearance and vital signs. In addition, qualifying BRUE criteria must be met, including a distinct color change of cyanosis or pallor, an abnormal or absent breathing period, a change in muscle tone, and/or a change in alertness of the patient. The episode must have at least 1 of these event criteria present. If, after a thorough history and examination, the event cannot be explained by a specific medical diagnosis, it then meets the BRUE diagnosis. (3) If a diagnosis is made after this evaluation, such as suspected reflux, seizure, or feeding difficulties, the event is not categorized as a BRUE, and should be subsequently managed according to the presumed diagnosis. Figure 2 shows the BRUE algorithm. The most common diagnoses that have been associated with ALTE, and that should be ruled out before making a BRUE diagnosis, include gastroesophageal reflux in 20% to 54% of patients, respiratory tract infections in close to 8%, seizures in approximately 4% to 7%, serious bacterial infections have in 2% to 8% of infants, and implicated child abuse in 1% to 11%. (12)

The subject of child abuse as an underlying cause of an ALTE episode has been the topic of further research due to the difficulty in making the diagnosis and the risk of death associated with missing nonaccidental trauma. One study in particular reported mortality of 33% of all abused children who presented with an ALTE; in contrast, overall mortality with ALTE is reported to be approximately 1.3%. (13) These data should drive clinicians to maintain a high index of suspicion for nonaccidental trauma when evaluating infants. Examples of findings that should trigger further investigation into nonaccidental trauma include a developmentally inconsistent history, a witness who changes the event history, delays in seeking medical care for the patient,

TABLE 2. Differences Between SIDS and ALTE (10)

CHARACTERISTIC	ALTE	SIDS
Incidence	Peaks 6–10 wk of age	Peaks at 3–5 mo of age
Risk factors	Prematurity, recurrent events, maternal smoking	Prone sleeping, co-sleeping, soft bedding, maternal smoking
Episodes happen more frequently	Awake	Asleep
Change in incidence after back to sleep campaign	None	30%–50% decline
Demographics	Boys = girls	Boys > girls
Maternal age	Follows the distribution of the normal population	Younger maternal age is associated with an increased incidence
Weight for gestational age	Incidence not increased in small for gestational age infants	More common in infants small for gestational age

ALTE=apparent life-threatening event, SIDS=sudden infant death syndrome.

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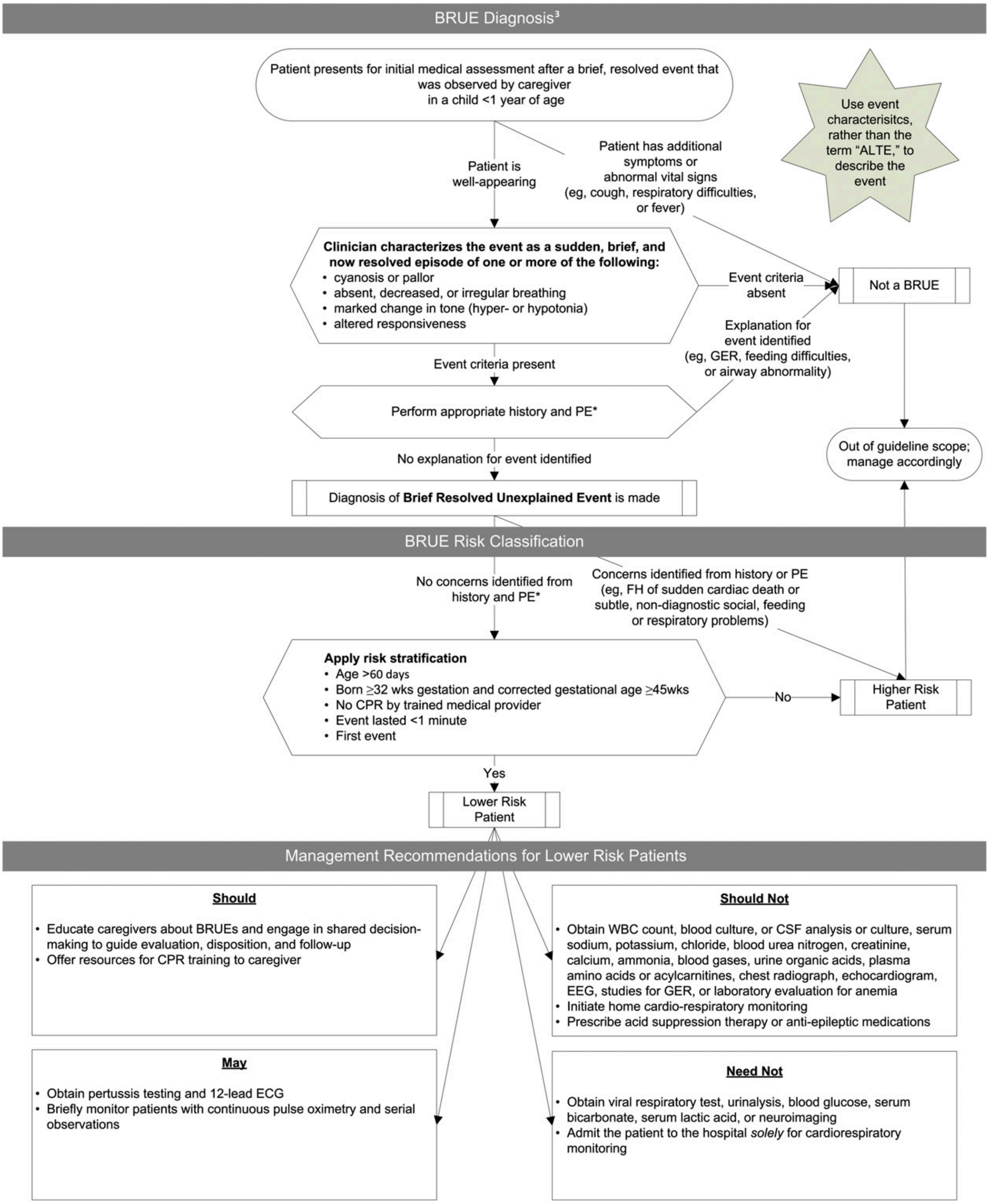
BRUE Diagnosis³
Patient presents for initial medical assessment after a brief, resolved event that was observed by caregiver in a child <1 year of age
Use event characterisitcs, rather than the term "ALTE," to describe the event
Patient is well-appearing
Patient has additional symptoms or abnormal vital signs (eg, cough, respiratory difficulties, or fever)
Clinician characterizes the event as a sudden, brief, and now resolved episode of one or more of the following:
• cyanosis or pallor
• absent, decreased, or irregular breathing
• marked change in tone (hyper- or hypotonia)
• altered responsiveness
Event criteria absent
Not a BRUE
Explanation for event identified (eg, GER, feeding difficulties, or airway abnormality)
Event criteria present
Perform appropriate history and PE*
No explanation for event identified
Out of guideline scope; manage accordingly
Diagnosis of Brief Resolved Unexplained Event is made
BRUE Risk Classification
No concerns identified from history and PE*
Concerns identified from history or PE (eg, FH of sudden cardiac death or subtle, non-diagnostic social, feeding or respiratory problems)
Apply risk stratification
• Age >60 days
• Born ≥32 wks gestation and corrected gestational age ≥45wks
• No CPR by trained medical provider
• Event lasted <1 minute
• First event
No
Higher Risk Patient
Yes
Lower Risk Patient
Management Recommendations for Lower Risk Patients
Should
• Educate caregivers about BRUEs and engage in shared decision-making to guide evaluation, disposition, and follow-up
• Offer resources for CPR training to caregiver
Should Not
• Obtain WBC count, blood culture, or CSF analysis or culture, serum sodium, potassium, chloride, blood urea nitrogen, creatinine, calcium, ammonia, blood gases, urine organic acids, plasma amino acids or acylcarnitines, chest radiograph, echocardiogram, EEG, studies for GER, or laboratory evaluation for anemia
• Initiate home cardio-respiratory monitoring
• Prescribe acid suppression therapy or anti-epileptic medications
May
• Obtain pertussis testing and 12-lead ECG
• Briefly monitor patients with continuous pulse oximetry and serial observations
Need Not
• Obtain viral respiratory test, urinalysis, blood glucose, serum bicarbonate, serum lactic acid, or neuroimaging
• Admit the patient to the hospital solely for cardiorespiratory monitoring

Figure 2. Brief resolved unexplained event (BRUE) algorithm.
ALTE=apparent life-threatening event, CPR=cardiopulmonary resuscitation, CSF=cerebrospinal fluid; ECG=electrocardiography, EEG=electroencephalography, FH=family history, GER=gastroesophageal reflux, PE=physical examination, WBC=white blood cell.

patient history of recurrent ALTEs/BRUEs, a family history of ALTE/BRUE, and previous calls to emergency medical services. On physical examination, signs such as bruising, oropharynx or frenulum damage, retinal hemorrhages, and subconjunctival hemorrhages should raise concern for child abuse. A recent study introduced the possibility of screening patients with ALTEs for abuse with dilated fundoscopic examination. In this study, 1 of 73 infants (1.4%) exhibited

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retinal hemorrhages. (11) It is important to mention that this patient was otherwise asymptomatic on presentation and was later found to have several fractures. (13) Although retinal hemorrhages may be helpful in identifying patients who have experienced abusive head trauma, it may not aid in the diagnosis of a factitious illness or imposed suffocation. In these instances, the recurrence of events is what will usually guide the clinician to suspect these diagnoses. Studies have reported that the occurrence of child abuse in recurrent ALTEs has varied between 10.6% and 16.7%. (11)

BRUE Risk Stratification

Once a BRUE diagnosis is made, the clinician needs to determine whether the infant qualifies in either the lower-risk or higher-risk classification group (Fig 3). This risk category should guide the decisions for appropriate evaluation and management based on specific concerns elicited. Previous studies in patients with ALTEs have shown that extensive, wide-ranging laboratory or radiologic tests that are not guided by clinical suspicion are of low yield, and the probability of a contributory result is very unlikely. The BRUE guidelines, as well as previous ALTE recommendations, state that the most important diagnostic investigation is to perform a thorough history and physical examination. A detailed description of the episode should be obtained from any caretaker or medical professional witness. A comprehensive interview includes obtaining a history of preceding illness and an extensive medical, family, social, and environmental history, as well as always screening for child abuse. The clinician should document the state of the patient before, during, at the conclusion of, and after the event. (3) A thorough initial evaluation may increase the index of suspicion for a specific diagnosis and, therefore, exclude a patient from the BRUE risk classification. These diagnoses include, but are not limited to, vital sign instability; growth curve abnormalities; altered infant alertness and responsiveness to the environment, craniofacial anomalies, nasal congestion; abnormal auscultation findings; palpation of masses; tenderness or organomegaly; genital abnormalities; gross motor movement, reflex, and tone irregularities; and any signs of trauma, bruising, injury, or pain. (3) If any findings lead to concern, the event does not qualify as a lower-risk BRUE but rather as a higher-risk BRUE. A list of possible differential diagnoses to consider by systems in lower- and higher-risk BRUE are detailed in Table 3.

Lower-Risk BRUE. A lower-risk BRUE is an event that after a thorough history and comprehensive examination yields no concerning findings in a patient who is older than 60 days and was born at 32 to 45 weeks' gestational age. The event must also be the first episode of its kind, must not have required cardiopulmonary resuscitation (CPR) by a medical professional, and have lasted for less than 1 minute (Fig 3). All of these parameters must be met to be considered a lower-risk BRUE. Patients who qualify for the lower-risk category are less likely to have an undiagnosed life-threatening condition or a recurrence of an episode. As such they have a decreased risk of adverse outcomes and do not warrant hospitalization or a broad clinical evaluation. (3) This category assumes that clinicians have screened for social risk factors, and in particular for child abuse. The new guidelines offer recommendations for this specific population of patients based on current available evidence.

All families of lower-risk patients should participate in shared medical decision making to guide evaluation and ensure follow-up. This entails the clinician, after taking a careful history and conducting a thorough physical examination, discussing his or her findings with caregivers and educating them about a lower-risk BRUE. There are handouts available for parents and caregivers at the AAP Pediatric Patient Education website. (14) Appropriate and timely follow-up with a clinician should be established for a safe transition of care, ideally before discharge. Families should also be offered CPR training resources.

The guidelines state that lower-risk patients do not need admission for observation solely for cardiorespiratory monitoring. This is probably the most considerable change from previous ALTE guidelines. The authors suggest that infants with a lower-risk BRUE may be briefly monitored with continuous pulse oximetry and serial observations that can be performed in an outpatient setting from 1 to 4 hours. Furthermore, based on available evidence, it is optional to obtain a 12-lead electrocardiogram (ECG) on lower-risk patients. This recommendation is based on ALTE studies that looked at the use of screening ECGs. The review authors found that there was a high negative predictive value (96%–100%) of ECG screening for cardiac disease in ALTE cases. These data, together with the wide availability of ECGs and the severe, potential outcomes of certain arrhythmias or cardiac pathology if left undiagnosed, lend to the endorsement of considering ECGs in the lower-risk BRUE group. (3) Another recommendation is to consider testing for pertussis infection because it can cause events such as apnea, irregular breathing patterns, and cyanosis or pallor in infants who may not yet exhibit signs of a respiratory infection. However, it is cautioned that clinicians consider local pertussis infant and maternal vaccination rates, community prevalence of this disease, exposure history, and availability of timely testing. Because a positive finding of pertussis would change management, testing should be considered in the appropriate patient setting. (3)(12)

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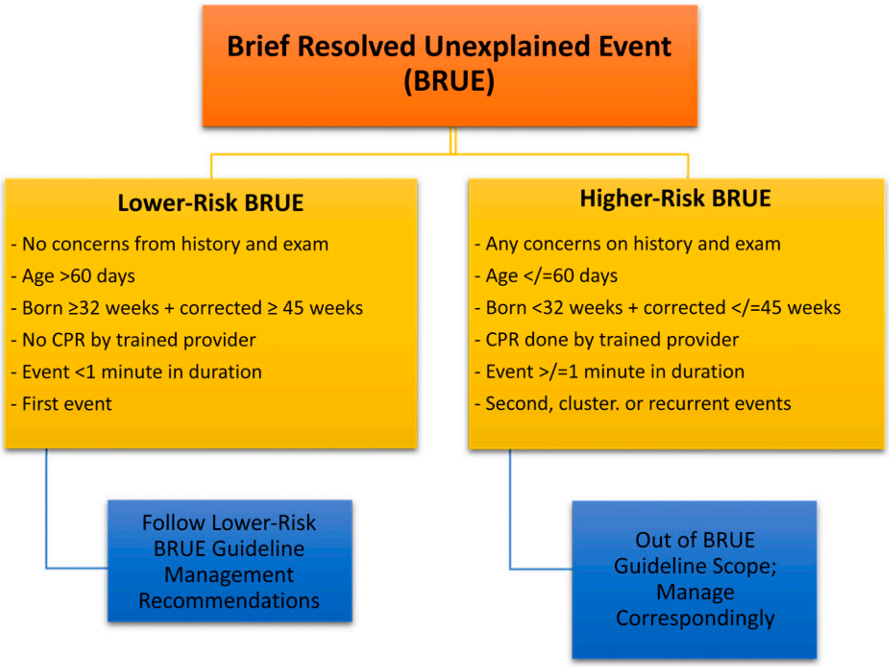
Brief Resolved Unexplained Event (BRUE)
Lower-Risk BRUE
- No concerns from history and exam
- Age >60 days
- Born ≥32 weeks + corrected ≥ 45 weeks
- No CPR by trained provider
- Event <1 minute in duration
- First event
Higher-Risk BRUE
- Any concerns on history and exam
- Age </=60 days
- Born <32 weeks + corrected </=45 weeks
- CPR done by trained provider
- Event >/=1 minute in duration
- Second, cluster. or recurrent events
Follow Lower-Risk BRUE Guideline Management Recommendations
Out of BRUE Guideline Scope; Manage Correspondingly

Figure 3. Brief resolved unexplained event (BRUE) lower-risk versus higher-risk classification. CPR=cardiopulmonary resuscitation.

Guidelines also strongly recommend against obtaining a complete blood cell count with a differential count (infection and anemia evaluation), blood culture, cerebrospinal fluid analysis or culture, complete metabolic panel, blood gases, genetic screening, viral respiratory testing, urinalysis by bag or catheter, and glucose, bicarbonate, and lactic acid studies. It is also noted that these patients do not need hospitalization for monitoring vital signs, chest radiography, echocardiography, electroencephalography, polysomnography, brain imaging, or gastric reflux diagnostics or any medications for seizures or gastrointestinal reflux. Patients should not be routinely discharged from the hospital with an apnea monitor. The AAP also endorses that physicians encourage and advocate for basic life support teaching for all caregivers. CPR training does not increase parental anxiety and, on the contrary, can result in empowering caregivers by equipping them with the knowledge of practical skills they may use during emergency situations, once the child is discharged home. (3)

Higher-Risk BRUE. A higher-risk patient is one who was diagnosed as having a BRUE but does not meet all of the lower-risk stratification criteria. If an event meets any of the following descriptions, it is considered a higher-risk BRUE. This includes patients who, after a thorough history and examination, it is determined that there is a concerning aspect that should be further investigated but the finding does not lead to an alternate definite diagnosis. If the child is younger than 60 days or was born at less than 32 weeks and has a corrected gestational age of less than 45 weeks, the patient belongs in the higher-risk group. If the event occurs more than once, or lasts for more than 1 minute, or CPR was performed by a trained provider, the child is also considered higher risk.

At this time, insufficient data are available to help guide clinicians in the management of this population. Extensive testing and hospital admission are not necessary for all patients in this group. Each case should be managed individually and follow a clinical decision-making process based on the provider's suspicion until further guidelines are available. The management and evaluation of a higher-risk BRUE should be based on pertinent patient history and clinical findings and should be performed in the context of shared decision making with the caregiver(s). In general, when presented with a higher-risk patient, it is helpful to reconsider potential differential diagnoses that would classify the event more accurately. (3)

SAFE INFANT SLEEP RECOMMENDATIONS AND APNEA MONITORS

In November 2016, the AAP updated their recommendations for SIDS and sleep-related infant deaths, such as suffocation, entrapment, and asphyxia. As previously stated, when the "Back to Sleep" campaign was begun in

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TABLE 3. **Differential Diagnosis of Lower- or Higher-Risk BRUE (3)**

OTOLARYNGOLOGIC	**PULMONARY**
Maxillary hypoplasia	Aspiration
Micrognathia	Asthma
Macroglossia	Foreign body
Choanal atresia	Congenital airway anomalies/malacia
Pyriform aperture stenosis	Infection
Laryngomalacia/anomalies	Hemorrhage
Subglottic stenosis	Upper and lower respiratory tract infection
Tracheomalacia/anomalies	
Adenotonsillar hypertrophy	
Obstructive sleep apnea	
Vasovagal response	
Unintentional suffocation	
GASTROINTESTINAL	**INFECTIOUS**
Gastroesophageal reflux	Bronchiolitis
Dysphagia/choking	Pneumonia
Esophageal dysmotility	Croup
Laryngeal chemoreflex	Upper respiratory tract infection
Bowel obstruction	Urinary tract infections
Gastroenteritis	Sepsis
Tracheoesophageal fistulas	Meningitis
Esophageal foreign body	Gastroenteritis
Intussusception	Viral syndrome
	Specific organisms (pertussis, RSV, and other respiratory viruses)
CARDIOVASCULAR	**GENETIC/METABOLIC**
Channelopathies (prolonged QT syndromes, Brugada syndrome, short QT syndrome)	Inborn errors of metabolism (fatty acid oxidation disorders, urea cycle disorders)
Congenital heart disease	Mitochondrial disorders
Cardiomyopathy/myocarditis	Electrolyte disturbance
Vascular ring/sling/compression	Hypocalcemia
Ventricular pre-excitation (Wolff-Parkinson-White syndrome)	Hypoglycemia
Arrhythmia	
Sepsis	
Syncope	

Continued

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TABLE 3. (Continued)

NEUROLOGIC	CHILD MALTREATMENT
Seizures	Abusive head trauma
Stroke	Caregiver-fabricated illness (also known as Münchausen by proxy and medical child abuse)
Intracranial mass lesion	Intentional suffocation
Brain/intracranial structural or vascular abnormality	Poisoning
Intracranial hemorrhage	Medical neglect
Hydrocephalus	
Neuromuscular disorder	
Congenital central hypoventilation syndrome	
Apnea of prematurity	
Infant botulism	
Demyelinating disorder (transverse myelitis, multiple sclerosis, acute disseminated encephalomyelitis)	
TOXIN EXPOSURE	**MISCELLANEOUS**
Medication adverse effect	Acrocyanosis
Substance exposure via human milk	Hypothermia
Environmental exposure	Breath-holding spell
Vaccine reaction	Idiopathic

BRUE=brief resolved unexplained event, RSV= respiratory syncytial virus.

the 1990s, there was a decrease of approximately 40% in infant sleep-related deaths, but since then the mortality rate has stayed about the same. It is important to note that safe sleep recommendations have not shown a decline in ALTE events, which gives further evidence that ALTE and SIDS have no causal relationship. The updated guidelines are intended for the general population and children up to 1 year of age. The policy statement delineates the strength of each of the 17 guidelines based on case-controlled studies because randomized trials cannot be conducted for SIDS. (1)

"A" Level Recommendations (Good-Quality Patient-Oriented Evidence)

These strong recommendations include supine position exclusively for every sleep (including naps) until age 1 year or until the infant can roll unassisted, back and forth from supine to prone positions. (1)(6) Sleep positioning has been found to be the "strongest modifiable risk factor for SIDS," and supine positioning "does not increase the risk of choking or aspiration, even in those infants diagnosed with gastroesophageal reflux." (6) Supine positioning applies to newborns after 1 hour of skin-to-skin care, preterm infants in NICU and home settings, and children with gastrointestinal reflux disease. Other sleep-related recommendations include using a firm sleep surface that conforms to Consumer Product Safety Commission (CPSC) standards, with only a thin, fitted sheet. Keeping soft items (including toys, pillows, crib bumpers, and positioners), loose sheets/blankets, hanging cords, and electric wires off the sleeping area are also important as these pose strangulation, suffocation, and entrapment risks. (1) A study that looked at accidental suffocation and strangulation in beds, which included 1,736 deaths in a 12-year period, found that the most common objects found to cause death were pillows in 24.5% of cases, mattresses in 21%, blankets in 13%, and walls in 15%. In addition, crib bumpers have been associated with infant mortality, and a ban has been supported by the AAP and members of the CPSC. (15) It is also prudent to avoid overheating of infants by

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overbundling or head covering. It is safer to use no more than 1 layer over what an adult would wear in the same environment, such as 1 layer of clothing with a wearable blanket. They also endorse parents to "room-share" with the infant up to at least 6 months of age, but infants should not "bed-share," which includes sleeping in the caregiver's bed, couches, or any type of chair. (1)

It is also important for all health-care providers, including staff in the nursery and the NICU, and any child care clinician to model and endorse the safe sleep recommendations to caregivers. It is important to approach parents in a nonjudgmental way and to continue to reaffirm safe sleep recommendations during a baby's first year. (1) These recommendations have been publicized as the "ABCs of Safe Sleep: Alone, Back, and Crib" at national, state, and local advocacy efforts and adapted by various agencies. "Alone" refers to only the infant being in the crib and excluding any caregivers, toys, pillows, blankets, or bumpers from the crib. "Back" refers to supine positioning for every sleep. "Crib" is for the use of a crib for infant sleep that adheres to CPSC standards. (16)

Breastfeeding is also a strong recommendation. In 2016, the authors of the AAP guidelines cited a meta-analysis of 18 studies on breastfeeding that showed reduced risk of SIDS. In this 2011 study, it was concluded that the breastfeeding was "protective against SIDS, and this effect is stronger when breastfeeding is exclusive." (17) An additional 2017 study by the same authors, published after the safe sleep recommendations, looked at what the duration of breastfeeding should be to show protection against SIDS. After conducting a multivariable pooled analysis, authors found that a minimum of 2 months of any breastfeeding, either exclusive or partial, was necessary to have significant protection against SIDS and that it decreased the risk by approximately 50%. (18) It was also found that "the protective benefits of breastfeeding increase as the duration increases," which helps to reinforce the AAP recommendations of breastfeeding for at least 6 months. (1)(18) These findings further encourage clinicians to reassure parents that any breastfeeding, whether exclusive or with formula supplementation, past the infant's age of 2 months significantly reduces the risk for SIDS. Moreover, pacifiers have also been shown to have a protective effect and as such should be used during daytime naps or nighttime sleep; however, the mechanism as to why pacifiers offer decreased SIDS risk is not yet known. A pacifier does not need to be reinserted if it falls out. Its use may be delayed in breastfeeding infants until breastfeeding is well established. Pacifiers should not be placed around the neck (pacifier necklace) or attached to the baby's clothes or a stuffed toy because pacifier use in this manner may cause strangulation or suffocation. (19)

In addition, "A" recommendations continue to advise all women to have regular prenatal care. Women should avoid any smoking, alcohol use, and illicit drug use during pregnancy and after giving birth because there is a proven increase in SIDS risk. (1) Children should follow the AAP and Centers for Disease Control and Prevention (CDC) immunization schedule, and it is important to emphasize this to families as part of SIDS prevention. (20) Data affirm that scheduled vaccinations are protective and do not contribute to SIDS risk. (21)

"B" Level Recommendations (Inconsistent or Limited-Quality Patient-Oriented Evidence)

Moderate-level recommendations reaffirm that the routine use of home apnea monitors in infants (including preterm and those with a sibling who died of SIDS) is not recommended because monitor use has not proved to reduce the incidence of SIDS. (1)(22) At this time, there are also no studies on the use of commercially available vital sign and sleep monitoring systems to reduce the risk of SIDS. (1) Caregivers ought to be advised that these devices have not been proven to prevent SIDS and may lead to false reassurance and false alarms that could lead to unnecessary tests, overdiagnosis, and increased caregiver anxiety. (23) Furthermore, supervised "tummy time" when an infant is awake is recommended to help with the development of motor milestones and avoidance of positional plagiocephaly, but prone positioning should otherwise not be used for sleeping. (1)

"C" Level Recommendations (Based on Consensus, Disease-Oriented Evidence, Usual Practice, Expert Opinion, or Case Series)

There is a paucity of evidence to suggest that swaddling reduces SIDS risk. (1) Some studies show that mortality may increase if the swaddled baby rolls or is placed into a position other than supine. (6)

Last, there should be continued research into the etiology of SIDS, the provision of training for all health-care workers on risk mitigation, improved surveillance, and establishment of evidence-based standardized protocols, as well as funding for public education campaigns. These continued efforts by many will help to achieve the ultimate goal of ending all SIDS events. (1)

ACKNOWLEDGMENT

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Summary

- By consensus, the term *apparent life-threatening event (ALTE)* should no longer be used, and the term *brief resolved unexplained event (BRUE)* should be applied only if the specific event criteria are met.
- By consensus, a BRUE must be further classified as lower risk (follow management recommendations as outlined) or higher risk (manage based on physician determination for the specific event).
- By strong evidence, ALTE/BRUE is not related to sudden infant death syndrome (SIDS), and interventions that have reduced SIDS have not reduced ALTE events.
- By strong evidence, clinicians should be aware of safe sleep recommendations for infants and reinforce their importance during infancy as part of routine anticipatory guidance to families.

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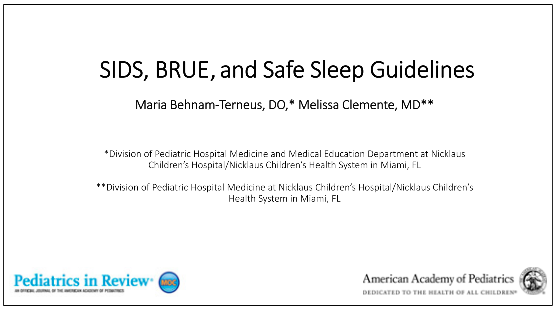

SIDS, BRUE, and Safe Sleep Guidelines

Maria Behnam-Terneus, DO,* Melissa Clemente, MD**

*Division of Pediatric Hospital Medicine and Medical Education Department at Nicklaus Children's Hospital/Nicklaus Children's Health System in Miami, FL

**Division of Pediatric Hospital Medicine at Nicklaus Children's Hospital/Nicklaus Children's Health System in Miami, FL

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1. A 4-month-old previously healthy child is found unresponsive in bed at 7 AM. The family calls 911 and the infant is rushed to the emergency department (ED) by emergency medical services with cardiopulmonary resuscitation in progress. After 15 minutes of resuscitative efforts in the ED, the child is pronounced dead. Investigation by the medical team, detectives, and later autopsy show no cause for the death. Based on the standard definitions currently in use, which of the following categories best describes this event?
   A. Apparent life-threatening event (ALTE).
   B. Brief resolved unexplained event (BRUE), higher risk.
   C. BRUE, lower risk.
   D. Sudden infant death syndrome (SIDS).
   E. Sudden cardiac death.
2. A 3-month-old infant is brought to the ED after an episode at home that caused brief choking and cyanosis. Her mom states that the infant was given her usual feed of 4 oz of formula from the bottle, and 30 minutes later the mother found her gasping and choking in bed, with formula coming from her mouth and bluish discoloration to her face and hands. The mother picked her up, patted her on the back, and cleared the airway. She gave her baby 2 breaths by mouth but did not perform cardiopulmonary resuscitation. The entire episode lasted approximately 30 seconds. She rushed her baby to the hospital, where the physical examination is completely normal. This infant was born at term and has never had an episode like this before. Growth and development are appropriate for age. Based on the available information, which of the following is the most likely diagnosis in this patient?
   A. ALTE.
   B. BRUE, high risk.
   C. BRUE, low risk.
   D. Choking with reflux.
   E. SIDS.
3. For the scenario described in question 2, which of the following is the best next step in the management of this patient?
   A. Hospitalize for cardiorespiratory monitoring.
   B. Obtain a chest radiograph.
   C. Order a complete blood cell count and metabolic panel.
   D. Order blood for genetic testing.
   E. Send the child home after reassuring the mother.
4. The mother of a 3-week-old boy who died of SIDS 6 months ago embarks on a mission to raise awareness and educate about ways to prevent SIDS. She establishes a nonprofit organization that provides a support group for mothers of infants who died of SIDS. She also provides educational awareness targeting parenting classes of expectant parents and providing them with ways to prevent the occurrence of SIDS. In her educational messages, she warns about which of the following conditions that have been positively associated with an increased risk of SIDS?
   A. ALTE.
   B. BRUE, high risk.
   C. BRUE, low risk.
   D. Pacifier use during daytime sleep.
   E. Placing the child in a prone position to sleep.

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5. The parents of a normal term newborn infant ask you about the use of infant monitors. They would like to use one for their child because a friend of theirs had an infant who died of SIDS. Which of the following is the best information you can give them about infant monitors and SIDS?
    - A. Home monitor use has substantially reduced the rate of SIDS in term infants.
    - B. Home monitors are recommended only for infants whose sibling died of SIDS.
    - C. Home monitors have been shown to reduce the rate of SIDS in children with congenital heart disease.
    - D. Home monitors have been shown to reduce the rate of SIDS in premature infants.
    - E. Home monitors have not been shown to reduce the rate of SIDS.

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Sudden Cardiac Death: A Pediatrician's Role

Benjamin H. Hammond, MD,* Kenneth G. Zahka, MD,* Peter F. Aziz, MD*

*Department of Pediatric Cardiology, Cleveland Clinic Children's, Pediatric Institute, Cleveland Clinic Foundation, Cleveland, OH

Education Gaps

1. There is a broad differential diagnosis to be considered in cases of sudden cardiac arrest, sudden cardiac death.
2. Timely diagnosis can circumvent progression to cardiac arrest in at-risk individuals.
3. All children should be screened and testing should be reserved for those with increased risk.

Objectives After completing this article, readers should be able to:

1. Assess risk of sudden cardiac arrest/sudden cardiac death (SCA/SCD) with a screening history and physical examination.
2. Identify the mechanisms of distinct etiologies of SCA/SCD.
3. Recognize findings consistent with risk of SCA/SCD on a 12-lead electrocardiogram.
4. Address the concerns and questions of individuals and families after SCA/SCD.

Sudden cardiac death (SCD) or sudden cardiac arrest (SCA) may occur in populations known to be at high risk or in individuals previously unrecognized to harbor underlying disease. This review focuses on the pediatrician's role in identifying the latter group.

DEFINITIONS

SCA is a "severe malfunction or cessation of the electrical and mechanical activity of the heart, resulting in almost instantaneous loss of consciousness and collapse" that precedes SCD. (1) SCD is defined as rapid, unexpected death from cardiac causes that occurs within 1 hour of symptoms. (2) SCD that is known to be secondary to a primary arrhythmia is termed *sudden arrhythmic death syndrome (SADS)*.

EPIDEMIOLOGY

SCA is a common cause of death in adults, with the annual incidence estimated to be approximately 100 per 100,000, with variation seen with age, sex, and race. (3) These deaths are predominantly associated with coronary artery disease. In individuals younger than 18 years, SCA is much less common, with an estimated

AUTHOR DISCLOSURE Drs Hammond, Zahka, and Aziz have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ACC	American College of Cardiology
AED	automated external defibrillator
ARVC	arrhythmogenic right ventricular cardiomyopathy
CPVT	catecholaminergic polymorphic ventricular tachycardia
ECG	electrocardiogram
HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter-defibrillator
LQTS	long QT syndrome
LVNC	left ventricular noncompaction cardiomyopathy
LVOT	left ventricular outflow tract
RV	right ventricle
SADS	sudden arrhythmic death syndrome
SCA	sudden cardiac arrest
SCD	sudden cardiac death
TdP	torsade de pointes
VA	ventricular arrhythmia
VT	ventricular tachycardia

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annual incidence of out-of-hospital cardiac arrest of 8.3 per 100,000 person-years. (4) Boys are more likely to be affected than girls, with a 2:1 incidence reported from Denmark. (5) In terms of race, incidence varies by diagnosis, as demonstrated by a recent autopsy study showing hypertrophic cardiomyopathy (HCM) to be more common in African American athletes and arrhythmogenic right ventricular cardiomyopathy (ARVC) to be more common in white athletes. (6) The etiologies of SCD have been explored by anatomical and molecular autopsy, with the most common positive finding being HCM. Autopsies performed on athletes with SCD report sizable groups of autopsy-negative sudden death. (6)(7) Given the potential for false-negatives on molecular autopsy, it is reasonable to consider inherited arrhythmias as potential diagnoses in these groups.

RECOGNIZING PATIENTS AT RISK FOR SCA/SCD

There has been an increased awareness of the risk of SCA/SCD in competitive athletes. Although this risk is not exclusive to athletes, competitive athletes have been shown to be at increased risk for SCA/SCD, which has led to the implementation of preparticipation screening. (8)(9) The pediatrician has the opportunity to identify risk factors for SCA/SCD as part of regular medical care of all individuals as well as during an athlete's preparticipation screening. The tools to identify those at risk for SCA/SCD include the patient's family and personal history and clinical examination. Those who have previously been diagnosed to be at risk for SCA/SCD should be followed regularly by a pediatric cardiologist. Asking each patient whether they have been diagnosed previously with a cardiac condition when establishing care can identify those previously discovered to be at risk. The American Heart Association has developed a 14-element screening recommendation for competitive athletes before participation in sports (modified and elaborated in Table 1). Use of electrocardiography (ECG) as a universal screening tool is controversial and is not currently recommended in the United States. (9) We recommend that these elements of screening be applied to all patients and not only for sports participation clearance.

The Challenge of Syncope

There is little doubt that syncope/presyncope is a common presenting problem to emergency departments, urgent care clinics, and general pediatrician offices. This accounts for up to 3% of all pediatric emergency department visits, with 15% to 25% of children and adolescents experiencing at least 1 episode of syncope before adulthood. Most of these events are vasovagal, and although they may result in injury, they are not a precursor for SCA/SCD. (13) Identification of an etiology for syncope that could result in SCA/SCD is essential.

TABLE 1. **Recommended Elements of the History and Physical Examination (9)(10)**

PERSONAL HISTORY	FAMILY HISTORY	PHYSICAL EXAMINATION
Chest pain[a] occurring with exertion?	Congenital heart disease?[b]	Cardiac auscultation (supine, sitting, and standing/squatting)[c]
Syncope/dizziness/lightheadedness with exertion?	Congenital deafness?	Femoral or pedal pulses with simultaneous radial pulse comparison
Early fatigue/shortness of breath?	Arrhythmias?[d]	Features of Marfan syndrome
Palpitations?	Long QT syndrome?	Resting blood pressure
History of hypertension?	ICD implantation?	
History of cardiac testing?	Sudden cardiac death before age 50 y?	
	Drowning?	
	Unexplained single-car accidents?	
	Syncope or seizures?	
	Cardiomyopathies ("abnormal heartmuscle")?	
	Marfan syndrome?	
	Other syndromes or known genetic mutations?	

ICD=implantable cardioverter-defibrillator.

[a] Chest pain is very unlikely to be cardiac in etiology; consider myocardial ischemia if there is an association with peak physical exertion.

[b] A first-degree relative of a patient with congenital heart disease is 3 to 80 times more likely to have congenital heart disease compared with the general population according to a Danish cohort study. (11)

[c] Systolic murmurs in hypertrophic cardiomyopathy are louder when standing from a squatting position.

[d] Genetic mutations leading to arrhythmias and other causes of sudden cardiac death have been identified in up to 30% of first-degree relatives. (12)

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Syncope that occurs with exertion should be considered a warning sign for SCA/SCD for every health-care provider. For example, a patient who was running on the cross-country team and fell unconscious in the middle of the run would be considered to have exertional syncope. A cross-country runner who stops after a long run, sits down, then stands up and loses consciousness would typically not be considered to have exertional syncope. The most likely etiology in the latter scenario would be vasovagal syncope. Vasovagal syncope will generally involve warning signs such as auras, dizziness, and lightheadedness; whereas exertional syncope will be sudden and unanticipated. Syncope in the water (swimming, diving, etc) presenting as drowning or near-drowning should also be considered exertional syncope with the potential for SCA/SCD until proved otherwise. Individuals with exertional syncope should avoid the triggers for their syncope and avoid unsafe situations where syncope could cause injury (ie, heights, driving, swimming) until they have been fully evaluated by a pediatric cardiologist.

Family History Is Key to Effective Screening

Experience has shown that we will not get a complete family history simply by asking, "Is there any family history of heart disease?" Table 1 provides specific points to address in the family cardiac history. Because most inherited arrhythmias and structural heart etiologies of SCA/SCD are autosomal dominant, all first-degree family members of the affected individual should be evaluated by, depending on age, a pediatric or adult cardiologist with expertise in the underlying disease. In this setting, we discourage screening by ECG or echocardiography testing alone.

ETIOLOGIES OF SCD

The 2012 AAP policy statement (10) on SCA describes the associated cardiac diagnoses grouped primarily as structural/functional and electrical. We have used these major categories to frame our discussion. The structural/functional group includes cardiomyopathies (HCM, dilated cardiomyopathy, left ventricular noncompaction cardiomyopathy [LVNC], and ARVC), myocarditis, coronary anomalies and atherosclerotic disease, aortopathies, congenital heart diseases, and pulmonary hypertension. The electrical group includes inherited arrhythmias (long QT syndrome [LQTS], short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia [CPVT]), Wolff-Parkinson-White syndrome, and the traumatic electrical phenomenon of commotio cordis. Table 2 gives an overview of these diagnoses with their ECG findings and major therapies.

Structural/Functional Etiologies of SCD

Hypertrophic Cardiomyopathy. HCM is the most common cause of SCD in young people, reported to be present in 1 in 500 of the general population. (14) A review of the US National Registry of Sudden Death in Athletes (1980-2011) found that 36% of the 842 confirmed cardiac deaths were due to HCM. (6) It is a disease involving a thickened left ventricle predominantly of the interventricular septum. The mitral valve can cause dynamic subaortic obstruction by anterior motion of the valve leaflets during systole coming into contact with the septum (systolic anterior motion). Individuals can develop left ventricular outflow obstruction leading to unexplained syncope with or without exertion, and eventually have symptoms of heart failure. The degree of outflow obstruction, however, is not an established risk factor for SCA. Mutations in the genes encoding cardiac sarcomeres can lead to significant myocardial remodeling and septal hypertrophy with resultant myocardial ischemia. Scar formation and disorganized myocytes make these patients prone to ventricular arrhythmias (VAs) with subsequent arrest. Medical therapy with β-blockers and calcium channel blockers is recommended in patients with symptomatic (angina, dyspnea) HCM. (15) An implantable cardioverter-defibrillator (ICD) may be indicated for patients determined to have significant risk factors. These risk factors include previous cardiac arrest, documented ventricular tachycardia (VT), a recent history of syncope, a family history of SCD associated with HCM, left ventricular wall thickness of at least 30 mm, and abnormal blood pressure response during exercise. Cardiac magnetic resonance imaging can elucidate degree of scar formation to assist in risk stratification. (16) Current sports participation guidelines for these individuals recommend avoidance of all competitive sports except those defined as low intensity because significant sympathetic activity may place them at greater risk for VT, although these same guidelines offer the opportunity to liberalize sports participation in selected low-risk individuals. (17) A personal history of shortness of breath, chest pain, or syncope with exertion can raise suspicion for this diagnosis, especially when combined with a family history of SCD, cardiac surgery in early adulthood, or ICD implantation in multiple generations.

Dilated Cardiomyopathy and LVNC. Two other forms of cardiomyopathy associated with SCA/SCD are dilated cardiomyopathy and LVNC. These pediatric cardiomyopathies have a reported incidence less than 1:100,000. (18) Dilated cardiomyopathy, involving progressive dilation of the ventricles with subsequently decreased systolic function, has a poor prognosis, with 40% of children undergoing cardiac transplant or dying within 5 years of diagnosis. There is a 5-year SCA/SCD incidence rate of 3% secondary to VAs. (19)

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TABLE 2. **Characteristics of Different SCA/SCD Etiologies**

SCA/SCD ETIOLOGY (PREVALENCE IN POPULATION)	PRINCIPAL MECHANISM OF SCA/SCD	ECG FINDINGS	TREATMENT
STRUCTURAL/FUNCTIONAL ETIOLOGIES			
HCM (1:500)	VAs	LVH with T-wave inversions in V4–V6	β-Blocker Myectomy, ICD for high-risk patients
DCM and LVNC (< 1:100,000)	VAs	Sinus tachycardia, LVH	Heart failure management ICD, heart transplant
ARVC (1:2,000-5,000)	Fibrofatty scar formation of RV leading to VAs	T-wave inversions and epsilon waves in the right precordial leads	β-Blockers, antiarrhythmics Ablation Heart transplant
Myocarditis (3:1,000)	VAs associated with myocardial dysfunction/inflammation (acute), scar (chronic)	Low voltages, sinus tachycardia, ST and T-wave changes; variable AV block	Supportive care Possible use of corticosteroids, IVIG ECMO, VAD, heart transplant
Coronary anomalies (1–6.5:1,000)	Myocardial ischemia leading to VAs	Myocardial ischemia with exercise, abnormal Q waves, ST changes	Surgical vs catheter-based intervention
Aortopathies (6.5:100,000 for Marfan syndrome)	Acute hemodynamic compromise	LVH	Angiotensin receptor blockers, β-blockers Surgery
Congenital heart disease (1:100)	Multifactorial: heart block, ventricular dysfunction → VAs	Possible AV or bundle branch block, widened QRS	Treat underlying anatomy May require arrhythmia surgery, ICD
PH (1:16,000)	Spontaneous VAs, dissection/rupture of pulmonary artery, PH crisis	RVH	Treat underlying anatomy and physiology (anti-PH medications)
ELECTRICAL ETIOLOGIES			
LQTS (1:2,500)	Torsade de pointes	Prolonged QTc	β-Blockers ICD, consider LCSD
SQTS (unknown)	VAs	QTc <330 ms, tall peaked T waves	QTc prolonging medications ICD implantation
Brugada syndrome (1:1000)	Torsade de pointes	Coved-type ST elevations V1,V2	Ablation ICD implantation for high-risk patients
CPVT (1:10,000)	Bidirectional VT	Normal at baseline, exercise-induced VT	β-Blockers, antiarrhythmics +/– ICD (can ↑ risk of refractory VF) LCSD
Wolff-Parkinson-White syndrome (4–6:10,000)	Rapid anterograde conduction of atrial fibrillation	Preexcitation (short PR interval) delta waves	β-Blockers Ablation
Commotio cordis (unknown)	Nonpenetrating precordial trauma → VAs	Normal	Resuscitation (high mortality)

ARVC=arrhythmogenic right ventricular cardiomyopathy, AV=atrioventricular, CPVT=catecholaminergic polymorphic ventricular tachycardia, DCM=dilated cardiomyopathy, ECG=electrocardiogram, ECMO=extracorporeal membrane oxygenation, HCM=hypertrophic cardiomyopathy, ICD=implantable cardiac defibrillator, IVIG=intravenous immunoglobulin, LCSD=left cardiac sympathetic denervation, LQTS=long QT syndrome, QTc=corrected QT interval, LV=left ventricle, LVH =left ventricular hypertrophy, LVNC=left ventricular noncompaction, PH=pulmonary hypertension, RV=right ventricle, RVH=right ventricular hypertrophy, SCA=sudden cardiac arrest, SCD=sudden cardiac death, SQTS=short QT syndrome, VA=ventricular arrhythmia, VAD=ventricular assist device, VF=ventricular fibrillation, VT=ventricular tachycardia.

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LVNC is a disorder of the left ventricular myocardium wherein compaction is incomplete, resulting in prominent trabeculations with deep recesses and 2 distinct layers of compacted and noncompacted myocardium. (20) Clinical features in both diagnoses range from severe ventricular dysfunction with end-stage heart failure to normal function without clinical features of heart failure. There is similarly a range of treatment options usually involving β-blockers, angiotensin-converting enzyme inhibitors, anticoagulants, and aldosterone antagonists, followed by mechanical support and transplant as indicated. Patients with LVNC have an increased risk of lethal VAs, with an associated SCA/SCD rate of 6%. (21) Individuals can present with chest pain and syncope that occur with exertion or with aborted cardiac arrest. Several more can be diagnosed by screening of family members.

Arrhythmogenic Right Ventricular Cardiomyopathy. ARVC has a prevalence in the general population of 1 in 5,000, with a prevalence of 1 in 2,000 individuals in Italy and Germany. It is an autosomal dominant disease caused by a genetic defect of the cardiac desmosomes leading to myocyte detachment and cell death predominantly involving the right ventricular (RV) myocardium. (22) There is remodeling of the cellular connections and replacement of the RV myocardium with "fibrofatty" scar tissue, which can be a substrate for VAs leading to SCD. The RV will become dilated and dysfunctional, with regional wall-motion abnormalities. (22) Presenting symptoms may be palpitations or exertional syncope. ECG can demonstrate T-wave inversions in the precordial leads (V_1–V_4), with decreased QRS voltages in the limb leads. Widening of the QRS complexes in the right precordial leads reflects an enlarged RV. Characteristic epsilon waves (small, peaked wave between the S and T waves) in V_1 and V_2 can be seen in patients with an advanced form of the disease (Fig 1A). Sympathetic activity has been associated with an increased risk of VAs in these patients such that these patients are recommended against participation in competitive sports. Heart failure can develop with dilation and dysfunction of the RV. Medical therapy has had modest success, although in patients with significant disease, medical therapy is refractory. Catheter ablation is therapeutic but not curative due to the progressive nature of this disease. Patients with recurrent VAs are ultimately listed for heart transplant.

Myocarditis. Autopsies of young athletes with SCD demonstrated that 7% of the cases were related to myocarditis. (6) It involves inflammation of the myocardium, which is usually secondary to a viral infection. Other potential etiologies include bacterial, fungal, or parasitic infections; hypersensitivity reactions; autoimmune disease; toxins; and Kawasaki disease. In the acute phase of the illness, myocardial edema, poor function, and acidosis can lead to VAs and SCA/SCD. As healing occurs, fibrosis develops (chronic myocarditis), which can be a substrate for VAs. SCD secondary to VAs may occur during the acute or chronic phase of the illness, even years after the initial diagnosis and treatment. It can be challenging to diagnose patients before the disease more fully manifests itself with rapid deterioration of ventricular function. Acute myocarditis typically presents with sinus tachycardia in conjunction with decreased cardiac function, causing symptoms of heart failure. Physical findings may include extra heart sounds due to abnormal filling in the setting of heart failure. In a recent multicenter study, 87% of patients with myocarditis survived with medical management without the need for transplant. (23) Extracorporeal membrane oxygenation or ventricular assist devices may be required with consideration of heart transplant in refractory cases. Given the difficulty in identifying these patients in the early acute phase of the illness, we

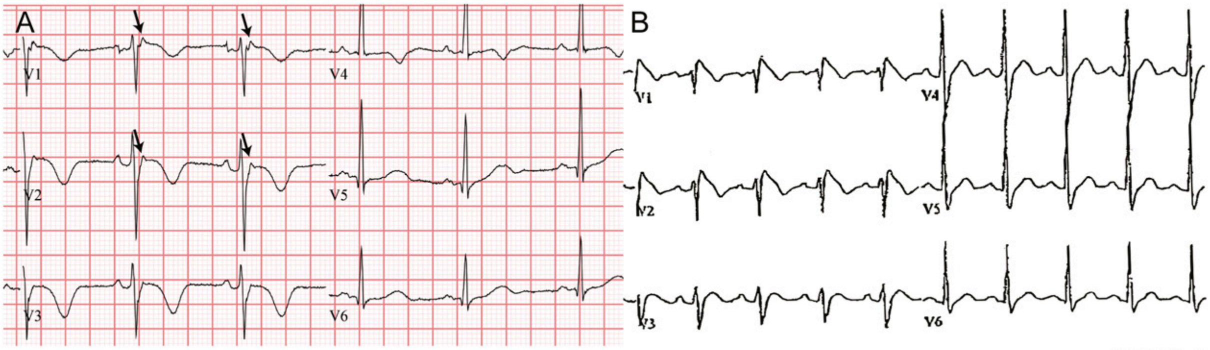

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Figure 1. A. Electrocardiogram in a teenager with multiple syncopal events during exercise shows T-wave inversions in leads V_1 through V_4 and epsilon waves (arrows) consistent with arrhythmogenic right ventricular cardiomyopathy. B. Electrocardiogram in a patient with Brugada syndrome with typical coved-type ST elevations in leads V_1 and V_2. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2018.

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recommend that athletes not participate in sports during intercurrent illness.

Congenital Coronary Anomalies. Congenital coronary anomalies were the second-most common cardiac etiology of sudden death in the US National Registry, composing 19% of those autopsied. (6) Typical normal coronary anatomy is a right and left coronary artery coming off their respective cusps in the region just above the aortic valve and traversing along the epicardium with branches diving to endocardium to provide perfusion of the cardiac muscle. Abnormal origin and courses of the coronary arteries can lead to exertional coronary ischemia. Anomalous coronary arteries may arise from the wrong aortic sinus, may course between the aorta and the pulmonary artery (interarterial course), or may course within the wall of the aorta (intramural course), which can potentially result in coronary insufficiency with exercise. This ischemia and resultant scar formation can predispose these patients to fatal VAs. The degree of coronary obstruction can be accentuated with exercise, and patients are, therefore, counseled to limit their level of exertion if they are having symptoms of chest pain during exercise. Symptomatic patients should be considered for surgery evaluation. Anomalous coronary arteries do not typically cause symptoms at rest. They may, however, cause exertional chest pain, syncope, dizziness, and palpitations that must be differentiated from more common etiologies. The key to diagnosis is either high-quality focused echocardiography or computed tomographic angiography. Unfortunately, family history and physical examination do not generally provide clues to these diagnoses.

Atherosclerotic Coronary Artery Disease. A rare cause of SCD in young patients is myocardial infarction secondary to premature atherosclerotic coronary artery disease. There is significant risk in patients with familial dyslipidemias. The AAP Guidelines for Cardiovascular Health and Risk Reduction in Children from 2011 recommend lipid profile screening as early as 2 to 8 years of age in patients who have a family history suggestive of early coronary artery disease or other individual risk factors. Universal lipid profile screening is recommended between ages 9 and 11 years, and then again between ages 17 and 21 years. (24) The standard practice of asking about a family history of early coronary artery disease (guidelines use a history of myocardial infarction, angina, stroke, coronary artery bypass graft, stent, or angioplasty before age 55 years in males and before age 65 years in females) can lead to early identification and preventive treatment for these patients. (24) Physical examination findings of xanthomas may aide in identifying these individuals as well.

Syndromic and Nonsyndromic Aortopathy. Progressive aortic dilation can be a silent process until presenting emergently or fatally with aortic dissection or rupture. This represents a small group of individuals (approximately 3%) in autopsy studies. (6) The individuals who are most at risk can be easily identified, having physical features of Marfan syndrome or Loeys-Dietz syndrome. In Marfan syndrome, a defective fibrillin-1 gene leads to a weakened extracellular matrix in the connective tissue of the aorta with the potential for dissection and rupture. The Ghent criteria are used to diagnose Marfan syndrome and they rely on systemic findings and family history. The pediatrician should ask whether there is any family history of aortic aneurysms, dissections, blindness, eye surgery, or diagnosed Marfan syndrome. Individual history should ascertain problems with eyesight (ectopic lentis) and history of spontaneous pneumothorax. Physical examination should evaluate for pectus deformity, scoliosis, reduced elbow extension, the wrist sign, the thumb sign, hindfoot deformity, pes planus, typical facial features, and reduced upper segment/lower segment and increased arm span/height. (25) These physical examination features compose much of the "systemic score" of the 2010 Revised Ghent Nosology for Marfan Syndrome, which can be calculated in the pediatrician's office using the systemic calculator provided by the Marfan Foundation (https://www.marfan.org/dx/score). Identification and referral of these individuals is essential for regular monitoring of aortic dimensions with cardiac imaging to determine need and timing of surgical intervention (aortic graft). Recent trials suggest that treatment with angiotensin receptor blocker therapy and β-blockers can slow aortic root dilation, suggesting a potential benefit from early recognition. (26) The only clue to nonsyndromic familial aortic aneurysm may be a family history of aortic dissection or rupture.

Congenital Heart Disease. In 1998, Silka et al (27) reported that the risk of SCD was 25 to 100 times greater in patients with congenital heart disease than in the rest of the population. The substrate for lethal VAs can be associated with the patient's underlying anatomy, such as can occur in patients with tetralogy of Fallot, or with the surgical scar from their repair. Individuals with tetralogy of Fallot are particularly at risk for SCA/SCD, which is believed to be associated with RV dysfunction predisposing to VAs. (28) A widened QRS interval is a factor in risk stratifying a patient with suspected or known VAs for ICD implantation. Long-term follow-up with a pediatric cardiologist is required for most repaired congenital heart defects, and some may require regular ambulatory ECG monitoring for ventricular ectopy. Even in this population,

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chest pain and syncope are more likely to be noncardiac, but when there is doubt, consultation with a pediatric cardiologist is encouraged.

Primary or Secondary Pulmonary Hypertension. Proposed etiologies of SCA/SCD include acute pulmonary hypertensive crisis leading to low cardiac output, compression of the coronary arteries by a dilated pulmonary artery, pulmonary artery dissection, massive hemoptysis, and rupture of the pulmonary artery. (29) An acute pulmonary hypertensive crisis may occur when the pulmonary vascular resistance acutely increases (may be in response to hypercarbia, acidosis), leading to right-sided heart failure, low cardiac output, and myocardial ischemia with potential for arrest. These patients are notorious for having poor outcomes after cardiac arrest. They are discouraged from participation in competitive sports. A prominent second heart sound can arouse suspicion, and an ECG with findings of RV hypertrophy should lead to an evaluation by a pediatric cardiologist.

Electrical Etiologies of SCA/SCD

Individuals at risk for SADS typically present with exertional syncope. Every individual presenting with exertional syncope should have an ECG. As we discuss etiologies of SADS diagnoses, we will review the ECG findings specific to patients considered to be high risk, which can guide referral to a pediatric electrophysiologist.

Long QT Syndrome. LQTS is a congenital rhythm disorder with an estimated prevalence of 1:2,500 that is associated with multiple genetic mutations that affect ion channel function. It is more common in white populations than in other races. (30) Prolongation of the QT interval can be secondary to channelopathies affecting repolarization. Specifically, the I_{Ks} potassium channel, the I_{Kr} potassium channel, and the I_{Na} sodium channel are predominantly affected secondary to genetic mutations. Prolongation of the repolarization phase of the cardiac myocytes can lead to a torsade de pointes (TdP) when a premature ventricular contraction occurs during the repolarization phase of the cardiac cycle. The autosomal recessive form of LQTS can be associated with congenital deafness. The most common types are identified as types 1, 2, and 3 (LQT1, LQT2, and LQT3). Characteristic LQTS triggers include exercise and increased sympathetic tone in LQT1, auditory and emotional triggers in LQT2, and sleep in LQT3. β-Blocker therapy, which acts to reduce sympathetic tone, can benefit patients with LQT1 and LQT2. Recent recommendations for sports participation have evolved as studies have demonstrated safety in sports participation for previously asymptomatic individuals on β-blocker therapy. (31) Individuals with a history of SCD, TdP on ECG monitoring, or a more high-risk type of LQTS are more likely to get an ICD device. Most patients with LQTS will not require ICD implantation. All

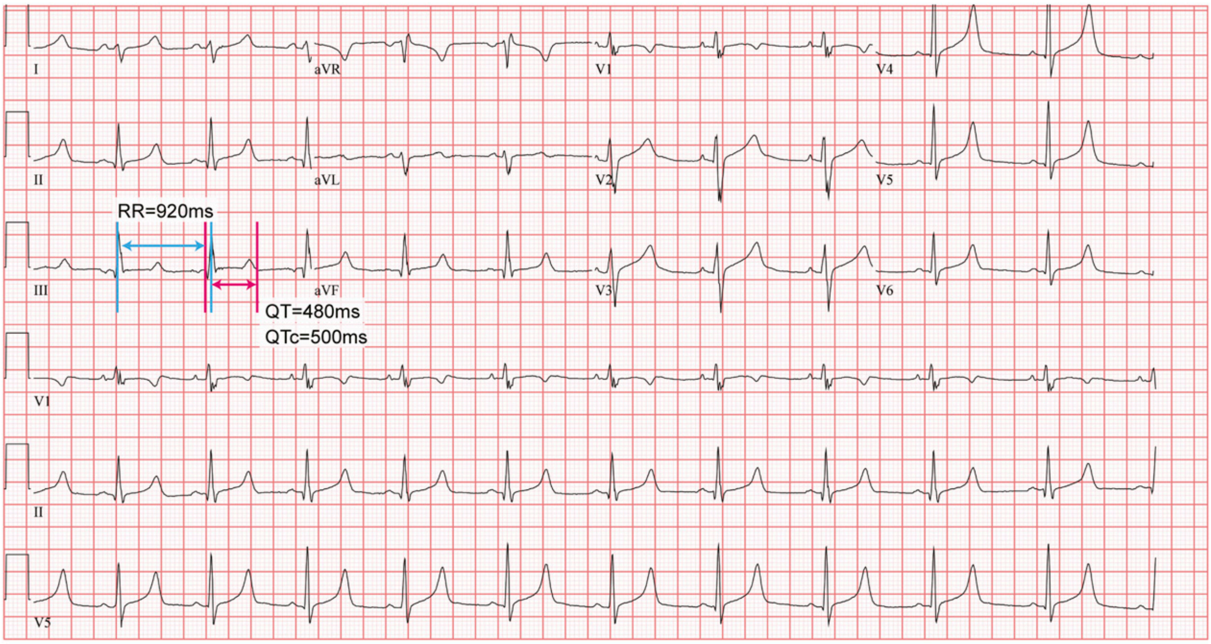

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Figure 2. Electrocardiogram in a patient whose father died of sudden cardiac death that shows QT prolongation. A clinician can count the small boxes (40 milliseconds each) between the lines drawn above and calculate the intervals. The Bazett formula $(QT/\sqrt{RR})$ can then be used to calculate the corrected QT interval (QTc). Machine reads often miscalculate this interval, and each clinician should, therefore, be comfortable with manual QTc measurement. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2018.

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individuals with known or suspected LQTS should be counseled to avoid multiple drugs that have been associated with QT prolongation (http://www.crediblemeds.org). Accurate measurement of the QT interval involves correcting for heart rate known as the Bazett formula: corrected QT interval (QTc) = QT interval/$\sqrt{}$RR interval (Fig 2). This is a valuable skill for every clinician to develop given the frequent inaccuracy of machine-generated reads. The Schwartz criteria (32) are used clinically to determine the probability of LQTS (Table 3). Genetic testing and screening ECGs are performed for first-degree family members after a diagnosis has been made.

Short QT Syndrome. A rare cause of SCD is short QT syndrome (SQTS) diagnosed by ECG as a QTc of 330 milliseconds or less with tall, peaked T waves. Short atrial and ventricular refractory periods have been shown to be associated with gain-of-function mutations of the potassium channels. SCD may occur secondary to VT or fibrillation. Antiarrhythmic medications that can prolong the QT interval can be therapeutic in these individuals. Many patients require ICD implantation.

Brugada Syndrome. Brugada syndrome has a prevalence of approximately 0.15% in adults in Asia (specifically Japan) and a 0.02% prevalence in the West. (33) It is diagnosed by a 12-lead ECG demonstrating coved-type ST elevations (Fig 1B) in the right precordial leads (V_1–V_3). If there is uncertainty regarding the ST segments in the precordial leads, repositioning of leads V_1 and V_2 to the second intercostal space may improve capture of the characteristic ST morphology. This finding has been associated with sudden death from polymorphic VT (TdP). A mutation of the *SCN5A* gene (I_{Na} sodium channel) occurs in 20% to 30% of individuals with Brugada syndrome. (34) This is the same gene that is affected in LQT3, but there is a gain of function in LQT3 compared with a loss of function in Brugada syndrome. Abnormal repolarization provides the substrate for TdP when a premature ventricular contraction comes during this phase of the cardiac cycle. These individuals can be asymptomatic and diagnosed by incidental finding on ECG. Those who present with symptoms (exertional syncope, SCA) or a spontaneous Brugada pattern on ECG are generally recommended to undergo ICD implantation. Similar to LQTS, these individuals should be counseled to avoid certain drugs (http://www.brugadadrugs.org).

CPVT. Individuals undergoing screening for LQTS with a history of exertional syncope, but without QTc prolongation, may be found to have CPVT. There is an estimated prevalence of 1 in 10,000. (35) Depending on the history, the pediatric cardiologist may perform a stress exercise test, which could induce VAs with CPVT. These arrhythmias are associated with calcium channel mutations (most commonly *RYR2*), which can lead to increased calcium release. This predominantly occurs during diastole and can lead to VAs when incited by premature contractions. β-Blockers have been shown to reduce VAs in these patients. Flecainide and left cardiac sympathetic denervation are additional treatment options for those with refractory events despite adequate β-blockade. (36) ICD implantation should be approached with caution because ICD discharges can be proarrhythmic due to the release of catecholamines, leading to a clustering of recurrent episodes of VT or ventricular fibrillation in a short period (“electrical storm”). (36)

Wolff-Parkinson-White Syndrome. Wolff-Parkinson-White syndrome is characterized by delta waves seen on ECG. A delta wave is a slurred upstroke of a QRS complex with a shortened PR interval, representing ventricular preexcitation by way of anterograde conduction through an accessory

TABLE 3. **LQTS Diagnostic Criteria (Abbreviated[a] Schwartz Criteria) (32)**

CRITERIA	PROBABILITY SCORE[b]
ECG findings	
QTc	
≥480 ms	3
460–479 ms	2
450–459 (males)	1
Torsade de pointes	2
Clinical history	
Syncope with stress	2
Syncope without stress	1
Congenital deafness	0.5
Family history	
Family members with definite LQTS	1
Unexplained SCD <30 y in a first-degree relative	0.5

ECG=electrocardiogram, LQTS=long QT syndrome, QTc=corrected QT interval, SCD=sudden cardiac death.

[a] *Certain elements of these criteria have been excluded to focus on findings easily recognized in a general pediatric clinic.*

[b] *Probability score: ≤1 point = low probability; 1.5–3 points = intermediate probability; ≥3.5 points = high probability.*

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pathway. Although narrow complex tachycardia can lead to hemodynamic instability, the major concern in these individuals is atrial fibrillation (Fig 3) leading to ventricular fibrillation due to rapid anterograde conduction through the accessory pathway. Patients can present with a narrow complex tachycardia with delta waves seen on ECG after conversion to sinus rhythm. Symptoms can be palpitations with abrupt onset of tachycardia with or without syncope. The role of the ECG in this diagnosis is to identify individuals with preexcitation who are, therefore, at risk for SCA/SCD. These individuals should stop participation in competitive sports until they are evaluated by a pediatric electrophysiologist. Ablation of the accessory pathway is the definitive treatment in these individuals.

Commotio Cordis. Commotio cordis is Latin in origin, meaning "agitation of the heart." This term has been used to describe the result of nonpenetrating trauma to the precordium resulting in VT or ventricular fibrillation. (37) There is nothing known of who, if anyone, is more at risk for commotio cordis. Prevention strategies are, therefore, used to avoid the type of trauma associated (ie, a baseball catcher or hockey goalie wearing chest protection). A recent review suggested that induced VT or ventricular fibrillation is determined by the location of the trauma (directly over the heart) and by the timing of the blow (occurring during early repolarization). (37) These patients are difficult to resuscitate, and mortality has been reported to be approximately 75%. Commotio cordis is more likely to occur in sports with projectiles, such as baseball, soccer, lacrosse, and hockey, although it can occur in any circumstance wherein there is blunt precordial trauma. It is important to counsel athletes and coaches regarding the dangers of direct blows to the chest and to use protective equipment when necessary.

ACUTE MANAGEMENT OF SCA

The period of effective defibrillation is believed to occur during the first few minutes after cardiac arrest. Regular training in the use of automated external defibrillators (AEDs) and cardiopulmonary resuscitation has been recommended for pediatricians and other medical staff. Pediatricians have been recommended to advocate for training in cardiopulmonary resuscitation and AED use in the community, in addition to effective placement of AEDs in the community. (38) In particular, families, schools, and

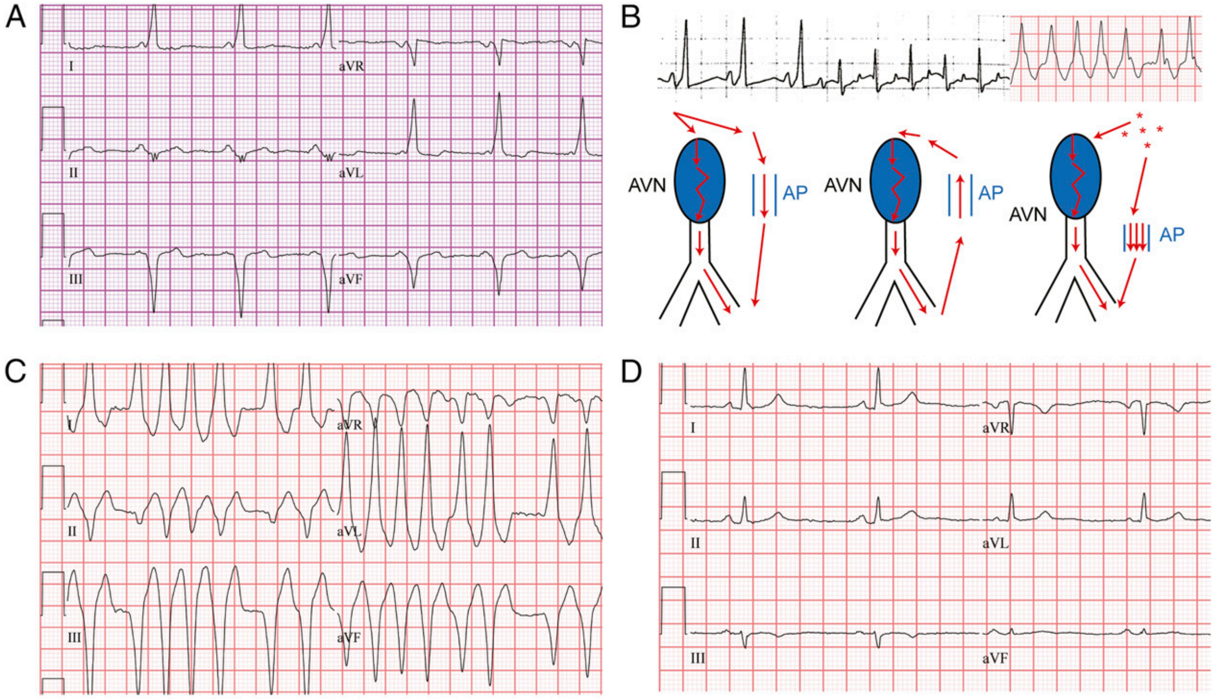

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Figure 3. A. Electrocardiogram (ECG) in an adult with Wolff-Parkinson-White syndrome diagnosed by the presence of delta waves. B. Illustration of conduction down the AV node (AVN) and the accessory pathway (AP). The first illustration shows conduction down both the AVN and the AP, leading to preexcitation of the ventricle (delta wave). The second illustration shows loss of delta waves with prolongation of the PR interval when conduction is down the AVN and up the AP. The third illustration demonstrates atrial fibrillation with rapid anterograde conduction down the AP. C. ECG in the same adult patient with wide complex, irregular tachycardia consistent with rapid anterograde conduction down the AP. D. ECG in the same adult patient with a normal PR interval and narrow QRS morphology after ablation of the AP. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2018.

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coaches of individuals who have been identified as high risk for SCA/SCD should be prepared to act in the event of SCA.

TARGETED SCREENING

Any individual suspected of having a high risk of SCA/SCD should be referred to a pediatric cardiologist as soon as possible. If the individual has been symptomatic, suspension of the activities that led to those symptoms is recommended until a thorough cardiology evaluation. Athletes and nonathletes alike with concern on ECG for QTc prolongation (LQTS), preexcitation (Wolff-Parkinson-White syndrome), coved-type ST elevations in V_1,V_2 (Brugada syndrome), T-wave inversions in the lateral precordial leads (HCM), or epsilon waves in leads V_1,V_2 (ARVC) should not return to play until they are evaluated by a pediatric cardiologist. We reemphasize the importance of screening all individuals with the recommended individual and family history questions discussed previously herein and a thorough physical examination. In the absence of the risk factors discussed, there is a group of individuals who need to be seen by a pediatric cardiologist for targeted screening. These are the first-degree relatives of SCA/SCD victims, so-called cascade screening. (39) The term *cascade* refers to the branching out of genetic testing that starts with first-degree family members of an SCD victim and subsequently extends to the first-degree family members of those who test positive, continuing in this pattern until all screened individuals have been identified. Genetic counselors and pediatric cardiologists can guide this screening process, which may include genetic testing, ECG, echocardiography, or exercise stress testing.

PSYCHOSOCIAL EFFECTS OF SCD

In the aftermath of SCD, family members are traumatized and often seek clarity from their pediatrician. A recent review by Ingles and James (40) gave recommendations for follow-up with these patient families in 3 defined stages: initial contact (ensuring family support), referral to a cardiac genetics clinic, and ongoing care (management of SCD-related anxiety). There are several online resources that may be helpful to families as well as to patients who survive SCA. Involvement in these groups and contribution to awareness groups or fundraisers can benefit grieving family members. Clinicians should have a low threshold for referral to a clinical psychologist when SCD-related anxiety is significant. Although genetic screening may initially increase a family member's anxiety in the short term, return to baseline functioning in the long-term is more likely with this knowledge. (40) In addition, clinicians should recognize and, as appropriate, attempt to alleviate feelings of guilt in family members of the deceased. Guilt may be felt for symptoms that went unrecognized, for encouragement of sports participation in an at-risk child, or even for being a carrier of the genetic mutation that led to a child's fatal disease. Taking time to educate and reassure can help families heal.

Summary

- It is critically important to recognize exertional syncope and to immediately refer these patients to a pediatric cardiologist.
- Use of the American Heart Association–recommended preparticipation history and physical examination should be included in a standard history and physical examination for all patients in this age group because nonathletes are also at risk for sudden cardiac death (SCD). (8)(9)
- All first-degree family members of victims of sudden cardiac arrest (SCA)/SCD should be screened for SCA/SCD by a pediatric cardiologist.
- Families of SCA/SCD victims can benefit from education by a well-informed pediatrician regarding the multiple etiologies of SCA/SCD and the difficulty in diagnosing these conditions before they occur.

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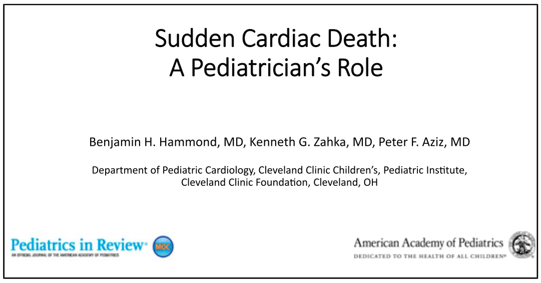
Sudden Cardiac Death:
A Pediatrician's Role

Benjamin H. Hammond, MD, Kenneth G. Zahka, MD, Peter F. Aziz, MD

Department of Pediatric Cardiology, Cleveland Clinic Children's, Pediatric Institute,
Cleveland Clinic Foundation, Cleveland, OH

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1. A 16-year-old African American male athlete experienced a sudden cardiac death (SCD) during a basketball game. The patient was a competitive basketball player who was a member of his high school basketball team. He was otherwise healthy with no medical conditions and was taking no medications. Family history is significant for an uncle who had an SCD at age 47 years. Among the following potential causes of SCD, which one is the most likely cause in this patient?
   - A. Arrhythmogenic right ventricular cardiomyopathy.
   - B. Coronary artery disease.
   - C. Hypertrophic cardiomyopathy.
   - D. Long QT syndrome (LQTS).
   - E. Supraventricular tachycardia.

2. A 10-year-old boy is brought to the clinic by his parents for a follow-up after an emergency department visit. The patient was seen in the emergency department a week ago with a 4-day history of fever, myalgias, cough, and congestion. He was diagnosed as having viral infection and was discharged home on supportive care. Today, the parents report that his symptoms have not improved. Earlier today he started having increased wet cough, vomiting, and decreased energy. He has been less active and was noted to have shortness of breath and wheezing. On physical examination today he is afebrile and in mild respiratory distress. Examination of the lungs shows diffuse coarse rhonchi and wheezes. There are subcostal and intercostal retractions. Heart examination shows sinus tachycardia, normal S1 and S2, loud S3, and an S4 gallop and no murmurs. His liver is palpated 2 cm below the right costal margin. Which of the following is the most likely diagnosis that explains the clinical presentation in this patient?
   - A. Acute bronchiolitis.
   - B. Acute myocarditis.
   - C. Acute hepatitis.
   - D. Aspiration pneumonia.
   - E. Reactive airway disease.

3. A 5-year-old boy is brought to the clinic for a school physical and health supervision visit. The patient was born with tetralogy of Fallot and is status post repair. He has normal growth and development and is taking no medications. The parents are concerned about him starting school and participating in physical education. They also wonder if they should allow him to play any sports in the future. Which of the following is the most appropriate recommendation to provide the parents at this time?
   - A. No restrictions on sports participation because the child has normal anatomy after repair.
   - B. No restrictions on sports participation if the patient has normal electrocardiographic and echocardiographic findings.
   - C. Restrict all sports participation indefinitely.
   - D. Restrict participation in contact sports only.
   - E. Routine cardiology follow-up with Holter monitoring for ventricular ectopy and for sports clearance decision.

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4. A 12-year-old girl was evaluated by a pediatric cardiologist after an episode of syncope during exercise. The episode occurred at the gym while she was watching TV while exercising on the treadmill. She was diagnosed as having LQTS . The parents are concerned and ask your opinion about potential triggers for the LQTS. In addition to exercise, which of the following could potentially be one of the triggers of LQTS?
   - A. β-Blockers.
   - B. Bright lights (visual stimulation).
   - C. Increased sympathetic tone.
   - D. Sleep deprivation.
   - E. Swimming in cold water.
5. You volunteer to provide the preparticipation clearance evaluation of the athletes at your local middle school. You use the American Academy of Pediatrics preparticipation screening questionnaire that is sent by the school to be completed by the parents before the sports physical examination. The questionnaire contains individual and family history questions along with history of past sports injuries. You review each completed questionnaire before you perform the physical examination. Which one of the following requires targeted screening by a pediatric cardiologist before the sports participation clearance decision?
   - A. All athletes before participation in competitive team sports.
   - B. All athletes before participation in high-intensity sports.
   - C. All athletes before their 12th birthday.
   - D. Athletes who are first-degree relatives of sudden cardiac arrest/SCD victims.
   - E. Athletes with a history of vasovagal syncope.

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Pediatric Head Trauma: A Review and Update

Rose N. Gelineau-Morel, MD,* Timothy P. Zinkus, MD,† Jean-Baptiste Le Pichon, MD, PhD*

**Division of Neurology and †Division of Radiology, Children's Mercy Hospital, Kansas City, MO*

Practice Gaps

There is still a considerable amount of confusion when it comes to managing concussions. An excessive number of head computed tomographic scans are being obtained for concussions, resulting in unnecessary exposure to ionizing radiation. Clinicians should be aware of the most recent guidelines for the management of concussion, including the need for imaging, and should be able to differentiate mild from moderate and severe traumatic brain injury.

Objectives

After completing this article, readers should be able to:

1. Differentiate a mild from a moderate or severe traumatic brain injury (TBI).
2. Acutely manage a child with a TBI, including deciding when further imaging is necessary.
3. Manage a child with a postconcussion syndrome and identify when referral to a specialist is necessary.

Traumatic brain injury (TBI) is the leading cause of death or severe disability in children older than 1 year. (1)(2) In a report to Congress published by the Centers for Disease Control and Prevention (CDC) in 2018, (3) the CDC reported the public health burden of TBIs. They noted that 640,000 emergency department visits and 18,000 hospital stays were directly related to TBI. The etiology of TBI varies among age groups. In the 0- to 4-year-old age group, the most common cause of TBI is falls. On the other hand, in the 15- to 24-year-old age group the distribution of injuries caused by falls, assault, and motor vehicle events are nearly equal. Epidemiologic studies have found that rates of TBI seen in the emergency department have increased in all age groups since 2001, with children 0 to 24 years old having the highest rates of TBI of all age groups. Children 0 to 4 years old have almost twice the rate of TBI compared with the next highest age group (15–24 years old), making pediatric traumatic brain injury an especially salient topic for the modern-day pediatrician. (4) Moreover, 61% of children with moderate to severe TBI experienced a disability. Estimates conclude that at least 145,000 children aged 0 to 19 years are currently living with long-term symptoms due to a TBI (likely an underestimate with underreporting of mild TBI [mTBI]), with

AUTHOR DISCLOSURE Drs Gelineau-Morel and Zinkus have disclosed no financial relationships relevant to this article. Dr Le Pichon has disclosed that he has served as a consultant for an AADC Deficiency Advisors Forum and as a medical legal expert and that he currently serves as the chair of the Subcommittee on Education for the American Academy of Pediatrics Section on Neurology Committee. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
AHT	abusive head trauma
CDC	Centers for Disease Control and Prevention
Child SCAT5	Child Sport Concussion Assessment Tool
CISG	Concussion in Sport Group
CT	computed tomography
DAI	diffuse axonal injury
FLAIR	fluid-attenuated inversion recovery
GCS	Glasgow Coma Scale
MRI	magnetic resonance imaging
mTBI	mild traumatic brain injury
TBI	traumatic brain injury

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symptoms extending far beyond their initial hospital visit into the following months and years. (3) Even children without overt neurologic deficits resulting from their TBI can demonstrate impairment in academic performance, attention and concentration, memory, and executive function, some of which only become apparent months or years after the initial injury. (4)(5)(6) The economic impact of TBI is substantial, with estimates ranging from $77.9 million per year in direct costs to more than $1 billion per year for TBI-associated hospitalizations. (5)

With all the associated morbidity and mortality, it is vital that pediatricians are educated in recognizing and treating TBIs and their sequelae. In this article, we aim to provide current evidence on the recognition, treatment, and rehabilitation of TBIs. We begin by discussing mTBI, typically manifesting as a concussion, and then discuss moderate and severe TBIs that are more often encountered in the emergency department or hospital setting.

MILD TBI

mTBI commonly manifests as concussion, and this is the focus of our discussion. However, it is also worth noting that even patients with more severe brain injury can exhibit signs and symptoms of concussion, and these should not be ignored. Concussion is a broad clinical diagnosis defined by the American Academy of Neurology as "a clinical syndrome of biomechanically induced alteration of brain function, typically affecting memory and orientation, which may involve loss of consciousness." (6) Due to various mechanisms of action for concussion, and the multiple disciplines involved, including neurology, sports medicine, rehabilitation medicine, and military medicine, there are multiple diagnostic criteria and treatment recommendations in place, which can make it challenging for the primary care provider evaluating a patient with a concussion. (7) Yet, concussion is a common complaint in children, occurring in approximately 692 of 100,000 children younger than 15 years, (8) indicating that an evidence-based, comprehensive plan for concussion diagnosis and management is imperative. (7)

In this section, we aim to summarize current recommendations on concussion evaluation and management for the general pediatrician based on guidelines for concussion management developed by the American Academy of Neurology, (6) the CDC, (9)(10) and the Concussion in Sport Group (CISG), an international multidisciplinary group of clinicians and researchers focused on concussion diagnosis and management. (11) The CDC recently published new guidelines on concussion management, and these recommendations are reflected herein. (10) Although concussion can be caused by any mechanical force on the brain, we focus on sports-related concussion because this is the focus of most research and clinical guidelines and is the most common presentation of concussion for the general pediatrician. (7) Note that although sports-related concussions have been studied most extensively, it is probable that most of the recommendations made thereafter apply equally well to concussions related to other accidental and nonaccidental injuries. In fact, in their most recent recommendations, the CDC (10) does not differentiate between these types of concussions as it relates to diagnosis and management.

Recognizing Concussion

The first step to treating concussion is recognition. The clinical phenotype of concussion can vary between patients, and it can be a challenge for the evaluating clinician to consider all the possible manifestations of concussion. One useful acronym is *COACH CV,* which was developed by Craton et al (12) and is based on the CISG guidelines. This acronym includes the most common clinical phenotypes of concussion: Cognitive dysfunction, Oculomotor dysfunction, Affective disturbances, Cervical spine disorders, Headaches, and Cardiovascular and Vestibular anomalies (Table 1).

Symptoms of concussion in these domains are broad and include impairment of memory or attention, blurred vision or abnormal extraocular movements, fatigue, mood changes, poor sleep, headaches, vestibular dysfunction, or heart rate variability (see Table 1 for a more extensive list of potential concussion symptoms). Of note, a patient with a concussion may have 1 or more of these symptoms. There is no loss of consciousness required for a diagnosis of concussion.

In their recent recommendations for the diagnosis and management of concussion, the CDC recommends using a validated symptom rating scale in the evaluation of concussion. (10) The most commonly used tools include the Child Sport Concussion Assessment Tool (Child SCAT5) developed by the CISG, (13) the Acute Concussion Evaluation developed by the CDC, (9) the Postconcussion Symptom Scale, (14) and the Graded Symptom Checklist. (15)(16) These tools use a Likert scale completed by the patient and/or parent to assess symptom severity, with a higher score indicating more severe symptoms. Although some of the scales, specifically the Child SCAT5, were developed for sports-related concussion, the symptoms of concussion are generalizable to other concussion etiologies as well. Studies have further analyzed these scales, attempting to identify the underlying symptom groups contributing to higher scores in concussed patients (eg, neurocognitive, somatic, emotional), with mixed conclusions. (14)(15)(17) In practice, it is best to choose a scale and get baseline testing, followed by

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TABLE 1. **Clinical Phenotypes of Concussion (COACH CV)**

	CLINICAL PHENOTYPE	SYMPTOMS	SPECIFIC TESTING
C	Cognitive function	Memory impairment, decreased attention and concentration, slowed processing speed	Neuropsychological testing (in person or computer-based, such as ImPACT testing)
O	Oculomotor dysfunction	Convergence insufficiency, blurred vision, abnormal saccades and/or smooth pursuit, photophobia	Visual acuity testing King-Devick test (assess saccadic eye movements)
A	Affective disturbances	Fatigue, sadness, irritability, sleep disturbance, poor concentration, emotionality	Depression screen
C	Cervical spine disorders	Neck pain, headaches, dizziness, balance difficulty	Neck range of motion Palpation of bones and muscles of the neck
H	Headaches	Migrainous, tension-type, or cervicogenic headaches	–
C	Cardiovascular anomaly	Exercise intolerance, heart rate variability or elevation, postural orthostatic tachycardia syndrome, autonomic dysfunction	Orthostatic vital signs Exercise stress test Tilt table testing
V	Vestibular dysfunction	Dizziness, vertigo, balance difficulties	Romberg test Tandem gait Vestibulo-ocular reflex Balance Error Scoring System (see the Child Sport Concussion Assessment Tool)

This table includes the common clinical phenotypes of concussion that patients may endorse on a symptom scale. Listed are the corresponding symptoms of each phenotype, as well as further testing that can be considered to assess each symptom. See Craton et al. (12)

testing at the time of injury and repeated testing throughout recovery to track changes in individual and total symptom scores. If symptoms in any 1 or more of the tested clinical domains are present, this suggests a diagnosis of concussion. (13)

If further delineation of symptoms is required, additional testing, either in the office or via a referral to the appropriate provider, can be considered. Some toolkits, such as the Child SCAT5, include further testing that can be performed by the provider to screen for certain concussion phenotypes. These include the Balance Error Scoring System, which assesses postural stability, and the Sensory Organization Test, which assesses the patient's equilibrium with altering visual and somatosensory inputs. However, these methods are not as sensitive at concussion diagnosis as the previously mentioned Likert rating scales. (6) Other targeted testing could include visual acuity for oculomotor dysfunction, orthostatic vital signs of cardiovascular dysfunction, or a detailed spinal neuromuscular examination to evaluate for cervical spine abnormalities (Table 1). (7)

Of note, computed tomography (CT) cannot be used to diagnose concussion and should generally be avoided to prevent unnecessary ionizing radiation exposure, although it may be used to rule out a more severe TBI, especially in patients with loss of consciousness, posttraumatic amnesia, persistent altered mental status, focal neurologic deficit, evidence of skull fracture, or signs of clinical deterioration. (6) The Pediatric Emergency Care Applied Research Network (PECARN) has established criteria that can be used in decision making for children presenting after a TBI. The clinical criteria for children 2 years and older include normal mental status, no loss of consciousness, no vomiting, nonsevere injury mechanism, no signs of basilar skull fracture, and no severe headache. If all of these criteria are met, they demonstrate a negative predictive value of 99.95% for clinically important TBI. Conversely, the presence of any 1 of these predictors has sensitivity of 96.8% in identifying clinically important TBI and indicates that further assessment with head CT is required. Criteria for children younger than 2 years are also included in the study. (18) Unfortunately, unnecessary head CT in children remains a common concern, and further education of community providers can help reduce this unneeded radiation exposure. (19)

Although clinical discretion is still required to make a concussion diagnosis, the previously mentioned tools can help identify symptoms and track recovery, aiding the clinician in decisions regarding return to play and when to pursue referral or further testing. With the typical natural history of concussion, an athlete's symptoms should return to baseline in 2 weeks for adults and in 4 weeks for children. (20)

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Rest and Return to Play

Once a concussion is diagnosed it is imperative that the patient is given the appropriate guidelines for rest and return to play/school. Previous recommendations for complete rest until symptom resolution are now outdated and likely stemmed from sports medicine literature in which there was a concern for second impact syndrome. Although this remains a concern, strict rest is not required for this entire period but rather guidelines now recommend complete rest for 24 to 48 hours, after which patients have a gradual return to full activity. In fact, a recent study comparing 2-day and 5-day strict rest periods in children with concussion demonstrated a slower resolution of symptoms in the group with a more prolonged rest. (21) After the initial rest period, children can follow a gradual return-to-activity protocol, which is outlined further in available toolkits, including the CDC Heads Up guidelines (9) and the Child SCAT5. The general strategy includes gradually increasing physical activity, beginning with nonaerobic daily activities and progressing through graduated steps until full return to sport (Table 2). The child should take at least 24 hours for each step of the plan, with return to the previous step for any worsening of symptoms. A similar progression can be used for return to school activities for children whose symptoms are exacerbated by mental activities, beginning with a few days of rest at home, followed by a gradual return to school full time. (13) Nonessential cognitive activities, such as playing video games, should be introduced as tolerated once a child is back to normal or near-normal physical routine.

There is some evidence to suggest that the period for full physiologic and metabolic recovery from concussion may extend beyond that for clinical symptom recovery and that a repeat concussion during this period could further prolong recovery. The NCAA Concussion Study on collegiate football players found that 11 of the 12 players with a repeat concussion in one season experienced their second concussion within 10 days of their initial concussion, indicating that athletes are especially prone to recurrent concussion during this period.

TABLE 2. **Return to Play Progression**

EXERCISE STEP	EXAMPLE ACTIVITIES	ACTIVITY TIME	GOAL OF EACH STEP
No activity	Complete physical and cognitive rest for 24–48 h		
Nonaerobic activity	Normal daily activities that do not provoke symptoms	–	Reintegrate into work and school activities
Light aerobic activity	Exercise bike, walking, light jogging at a slow pace (no weight lifting, jumping, or running)	5–10 min	Light activities leading to a mild increase in heart rate
Moderate activity	Jogging, brief running, moderate-intensity stationary biking, light resistance activities	Reduced from normal routine	Limited body and head movement
Heavy, noncontact activity	Running, noncontact drills, weight lifting, stationary biking	At or near normal routine	Intense activity without contact Cognitive activity during exercise can be added
Full contact	Normal full-contact physical activities	Normal routine	Return to full-contact activities
Competitive activities	Return to full competitive activities	Normal routine	No further restrictions in activity

The table is adapted from the Centers for Disease Control and Prevention Heads Up guidelines and the Child Sport Concussion Assessment Tool for returning to play. Each step should take a minimum of 24 hours. During the above progression, the child, family, and health-care provider should pay special attention to any new or worsening symptoms. If any symptoms worsen while exercising, the child should return to the previous step.

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(22) However, further details of time to complete physiologic recovery are not known and, at this time, it is only recommended that children have a "buffer" period of gradual return to full activity after complete symptom resolution. (23)

Although pharmacologic treatment has not been shown to facilitate recovery from concussion, it may be considered in patients who have longer recovery periods or whose quality of life is significantly affected by their symptoms. In these cases, treatment should focus on symptom management, including medications such as melatonin for sleep disturbance, nonopioid analgesics for acute headaches and amitriptyline or topiramate for headache prevention, and selective serotonin reuptake inhibitors or amantadine for emotional or cognitive effects, respectively. (24) Of note, in patients using pharmacotherapy, this could mask the symptoms of concussion, and these medications should be weaned or careful consideration should be given before returning to full play. (11)

Referral

Occasionally, the situation will still arise in which children do not have a complete recovery with the previously described strategies. Children with symptoms persisting beyond 4 weeks and adults with symptoms persisting beyond 2 weeks should be referred to a health-care provider specializing in concussion. (11) Studies have shown that higher symptom scores on immediate postconcussive testing can indicate more severe or prolonged postcognitive effects with a longer time for return to play. (25)

Certain preexisting conditions may delay concussion recovery, including history of postural orthostatic tachycardia syndrome, motion sickness, strabismus or ocular abnormalities, attention-deficit/hyperactivity disorder and learning disabilities, and mood disorders. These children may require additional school accommodations to facilitate their return. (26) Other factors such as history of previous concussions, more severe presenting or postconcussive symptoms, memory problems, fatigue/fogginess, and disorientation may also contribute to a more prolonged recovery. (6)(27) Some intrinsic factors, such as low socioeconomic status, Hispanic race, and high school age (especially in girls), also place children at risk for more prolonged symptoms compared with other patient populations. (10)(11)

Residual Effects

Unfortunately, approximately 10% to 15% of concussion patients have persistent symptoms beyond the first few weeks. (28) As recently as 2014, the *Diagnostic and Statistical Manual of Mental Disorders* criteria included a diagnosis of postconcussion syndrome, although this has now been renamed "major or mild neurocognitive disorder due to TBI." It is up to the clinician to consider the severity and functional disability of the patient when assigning a diagnosis. Postconcussive symptoms can be widely variable and depend on preexisting comorbidities, including neurocognitive disorders, vestibular dysfunction, affective symptoms, and medication/substance use. (27)

Additional evaluation and therapy should be considered for children with persistent postconcussive symptoms. Although most concussion patients will have normal cognitive function by 3 months after injury, some children could have cognitive deficits persisting up to 1 year, especially in the presence of a severe original injury, a history of previous concussions, and psychological risk factors. (29) These children should be referred for formal neuropsychological testing. Magnetic resonance imaging (MRI) can be more sensitive at detecting certain types of brain injury, such as diffuse axonal injury (DAI) or petechial hemorrhages, which are not detected in 25% to 30% of CT scans (see the "Management" subsection later herein). (30) Patients with vestibular or oculomotor dysfunction should be referred to the appropriate therapy for rehabilitation. Finally, the possibility of depression after concussion should not be ignored because it may often masquerade as cognitive or neurosensory dysfunction. (28)

Risk Reduction

General risk reduction for concussion centers around preventive safety measures to decrease risk of head injury. This includes the use of appropriate car seats, booster seats, or seat belts in automobiles; helmets while on bicycles or scooters; stair gates; and soft surfaces in play areas. (9)

However, the use of equipment in sports to protect against concussions is a controversial topic. The use of mouth guards does not seem to provide protection from concussion. (6)(31) Helmets and headgear have been shown to reduce the risk of concussion in skiing and snowboarding, but the effect in full-contact sports such as hockey and football has not been as conclusive. (31) This, in part, has led to the new rules for helmet contact implemented recently by the National Football League to reduce unnecessary risk of head injury in its players. (32)

Research on risk reduction for sports-related concussion has also focused on analyzing age, level of competition, sex, and type of sport to determine whether any individual factor can affect concussion symptoms and risk. A recent study found that females with concussion are more likely to report a higher level of symptoms and to experience postconcussive headaches, whereas males are more likely to experience loss of consciousness, confusion, and amnesia with a

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concussion. (33) Although rates of concussion in males are greater due to larger total numbers of athletes, concussion risk seems to be greater in female athletes playing soccer or basketball. In addition, for all athletes there seems to be a higher risk of concussion with American football and rugby compared with other sports, with baseball, softball, volleyball, and gymnastics having the lowest risk. (6)

There is also evidence that children experiencing a first concussion before age 10 years have approximately twice the risk of sustaining a subsequent concussion before age 18 years compared with patients experiencing their first concussion in adolescence. It is not known whether this is due to the early concussion itself, the duration of participation in contact sports, or intrinsic factors affecting an individual's concussion risk (eg, risk-taking behavior). (34)

Ultimately, health-care providers caring for amateur athletes with a history of an early concussion, recurrent concussions, or persistent concussive symptoms may need to discuss the previously mentioned evidence as well as implement formal neurologic and neuropsychiatric assessments to aid in the discussion of concussion risk management or possible retirement from play. (6)(35)

Second Impact Syndrome

One of the greatest concerns of parents and clinicians surrounding concussion is the threat of second impact syndrome. Second impact syndrome is described as a clinical syndrome of catastrophic cerebral edema that results when a second concussion occurs before resolution of symptoms from the initial concussion. (35) The second impact may be much less severe and not even a consequence of a direct impact to the head. (35) It is thought to be due to a failure of cerebral autoregulation coupled with a stress-induced catecholamine surge, leading to cerebral edema and consequent herniation, resulting in severe disability or death. (36) Although it seems to be extremely rare, a recent review of 17 cases reported in the literature from 1946 through 2015 noted an age range of 13 to 23 years, indicating that this is a syndrome that is particularly impactful in the pediatric population. (37) Although cases seem to be most common with repeated concussions within the first 2 weeks of the initial injury, children are considered to be at risk as long as they continue to be symptomatic from their initial concussion. This diagnosis has gained a lot of attention in the medical literature owing to its devastating consequences, yet there remains some controversy around its existence. It is known that diffuse cerebral swelling can occur after a single head injury, so the occurrence of a second impact to create the clinical syndrome may not be required. (38) Nonetheless, all concussion practitioners agree on the importance of complete resolution of symptoms before return to play because this will decrease the risk of prolonged postconcussive symptoms and the possibility of second impact syndrome. (31)

MODERATE AND SEVERE TBI

In this section we focus on moderate and severe TBI. Although there are several scales that have been used to differentiate mTBI from moderate and severe TBI, the most commonly accepted classification relies on the Glasgow Coma Scale (GCS), with moderate defined as a GCS score of 9 to 13 and severe as a GCS score less than 8 (39) (Table 3). These more severe injuries are differentiated from mTBI by the fact that they have clear imaging findings; mTBIs typically do not have any MRI or CT findings. Although TBI remains one of the leading causes of mortality and morbidity in children in the United States, the management of this entity continues to be applied quite unevenly despite the existence of American Academy of Pediatrics (AAP) recommendations. (40) The epidemiology of TBI was reviewed in the Introduction.

Pathophysiology of Pediatric Head Trauma

It is important to recognize that there are major differences between the pediatric brain and the adult brain in the pathophysiology of head trauma. Although it is generally true that the pediatric brain tends to be more resilient to focal lesions (stroke, surgical excision) as a result of plasticity, the opposite seems to be true when it comes to TBI. There is strong evidence that the younger a child is when experiencing a severe TBI, the longer he or she takes to recover. (41) Furthermore, the morbidity from TBI seems to be significantly higher in children than in adults. (42) This may be related to several factors, including incomplete myelination, the higher water content of the pediatric brain, and a critical period during development when synaptic pruning depends on complex physiologic mechanisms.

Space-Occupying Traumatic Injuries

The most urgent clinical factor associated with TBI is the rapid expansion of space-occupying lesions, including bleeds and progressing edema. Interestingly, posttraumatic hydrocephalus is much less common in children than in adults and can often be managed conservatively, obviating the need for decompression or evacuation. (43)

Space-Occupying Lesions: Bleeds

Bleeds caused by TBI can occur in several locations, including potential or anatomical spaces formed by the meninges and within the substance of the brain itself.

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TABLE 3. Pediatric Glasgow Coma Scale

	<1 Y	>1 Y		SCORE
Eye opening	Spontaneously	Spontaneously		4
	To shout	To verbal command		3
	To pain	To pain		2
	No response	No response		1
Motor response	Spontaneous	Obeys		6
	Localizes pain	Localizes pain		5
	Flexion withdrawal	Flexion withdrawal		4
	Decorticate	Decorticate		3
	Decerebrate	Decerebrate		2
	No response	No response		1
Verbal response	**0–23 mo**	**2–5 y**	**>5 y**	
	Smiles/coos	Appropriate words	Oriented	5
	Cries, consolable	Inappropriate words	Disoriented, confused	4
	Cries, inconsolable	Cries, inconsolable	Inappropriate words	3
	Grunts, agitated	Grunts	Incomprehensible sounds	2
	No response	No response	No response	1

Information from Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. Lancet. *1974;304:81–84.*

Epidural Hematoma. Epidural hematomas tend to be the result of arterial bleeds associated with skull fractures. These bleeds result from the accumulation of blood in the potential space formed by the junction of the dura mater and the skull (Fig 1). The classic example is a middle meningeal artery tear in the context of a temporal or parietal bone fracture. In this context, epidural bleeds can be catastrophic. Given the arterial nature of these bleeds they can lead to a very rapid mass effect with resulting herniation of the cerebral contents. However, it is important to recognize that epidural bleeds in children are usually much more forgiving than those in adults. (44) It is not completely clear why this might be, although in the study just cited smaller clots tended to be more frequent in younger children. Acute epidural bleeds are characterized by a hyperdense lens-shaped lesion on CT (Fig 2).

Subdural Hematoma. Subdural hematomas result from the accumulation of blood in the potential space between the dura mater and the arachnoid layers (Fig 1). These bleeds are usually caused by the rupture of bridging veins that traverse this space. They are quite frequent in infants, especially in the context of abuse. (45) They are also frequently caused by other forms of rapid shearing injuries to the brain, such as motor vehicle accidents. Subdural bleeds typically layer in a crescentic shape that, when acute, appears hyperdense on the CT scan of the brain (Fig 2).

Subarachnoid Hemorrhage. Subarachnoid hemorrhages result from the accumulation of blood in the subarachnoid space. As opposed to the 2 previous types of bleeds, subarachnoid hemorrhages occur in an anatomical space normally filled with cerebrospinal fluid (Fig 1). These bleeds are extremely common in the context of TBI and frequently cause seizures because blood is an irritant to the cerebral cortex. CT scans of an acute subarachnoid hemorrhage show hyperdense layering along the convexities of the cerebral cortex extending into the sulci and often the basilar cisterns (Fig 2).

Space-Occupying Lesions: Contusion and DAI

Contusions occur as a result of mechanical compression of the brain tissue, such as often occurs after a very rapid acceleration, and tend to have the greatest impact to the orbital frontal region. These types of injuries frequently cause a corresponding injury in the diametrically opposite side of the brain, likely a result of a low-pressure area of injury. These types of injuries are frequently referred to as *coup* and *contrecoup* injuries (Fig 2). Interestingly, the contrecoup injury is often more severe than the coup injury. (46)

DAIs are deep white matter track injuries typically caused by rapid rotational acceleration of the brain content. These injuries result in axonal damage and often axonopathy (axon disconnection). Technically, DAI can be diagnosed postmortem only. However, a patient presenting with a closed head injury caused by a high-velocity impact and found to have a GCS score less than 9 is highly likely to have sustained DAI. (47) These lesions can have devastating morbidities, especially when they affect white matter tracts arising from the frontal lobes and connecting to the limbic system. The frontal lobes are the seat of important higher cognitive functions, including premotor planning, executive function, motivational states, and social behaviors. (48) It has been well

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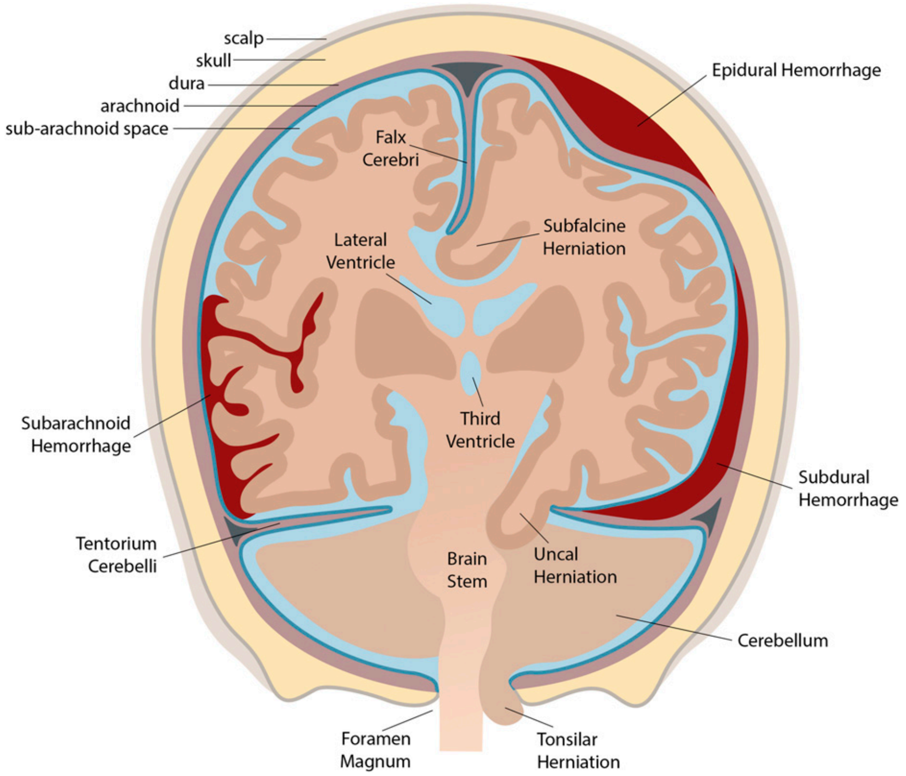

Figure 1. Schematic representation of intracranial hemorrhages and associated herniations. Note that for the sake of clarity, intraparenchymal hemorrhage, central herniation, and upward transtentorial herniation are not represented. (Illustration by Marie Le Pichon.)

established that subcortical injures in these regions can result in significant neuropsychiatric impairments, including lack of motivation, depression, disinhibition, aggressivity, and cognitive impairments, especially in the area of motor planning. Intraparenchymal hemorrhages as a result of head trauma also occur frequently in the context of DAI, either as microbleeds or as much larger hemorrhagic lesions (Fig 2).

Herniation Syndromes

Herniation syndromes occur as a result of a rapidly growing space-occupying lesion (over hours to days), such as a hemorrhage or developing edema. Herniation of the brain contents can occur around any of the major fixed intracranial structures, including the tentorium cerebelli (transtentorial or uncal herniation), the falx cerebri (cingulate or subfalcine herniation), and the foramen magnum (tonsillar herniation). Each of these herniation syndromes has clinically distinct presentations (Fig 1 schematically illustrates each type of cerebral herniation; see also Table 4). It is important to emphasize that the herniation itself is a consequence, not the cause, of the clinical symptoms observed. The cause of the syndrome is in fact the downward pressure on the individual anatomical structures of the cingulate gyrus, midbrain, and medulla. (49)

Transtentorial Herniation

Transtentorial herniation is probably the most common herniation in the context of TBI. It occurs as a result of a mass effect in the supratentorial (above the tentorium cerebelli) region. Transtentorial herniation can be unilateral (uncal herniation) or bilateral (central herniation) (many authors refer to a bilateral tentorial herniation as *transtentorial*).

Unilateral (Uncal) Herniation. If there is a unilateral compression from a bleed or hemispheric edema, there is a risk of uncal herniation. In this case, the space-occupying lesion forces a displacement toward the opposite side to the lesion, resulting in compression of several critical structures below the tentorial incisura (ridge formed by the tentorium cerebelli). Critical structures compromised in this syndrome include the oculomotor nerve (CNIII) and the main motor pathways (pyramidal tracts). As a result, one will observe a unilateral mydriasis that will be ipsilateral to the herniation (compression of cranial nerve III) but contralateral to the lesion and a hemiparesis that will be contralateral to the herniation (compression of the pyramidal tracts before the decussation of the pyramids) but ipsilateral to the lesion. A classic pathologic finding that has been described in this context is the Kernohan notch, caused by compression of the cerebral peduncle against the tentorium opposite to the side of the space-occupying

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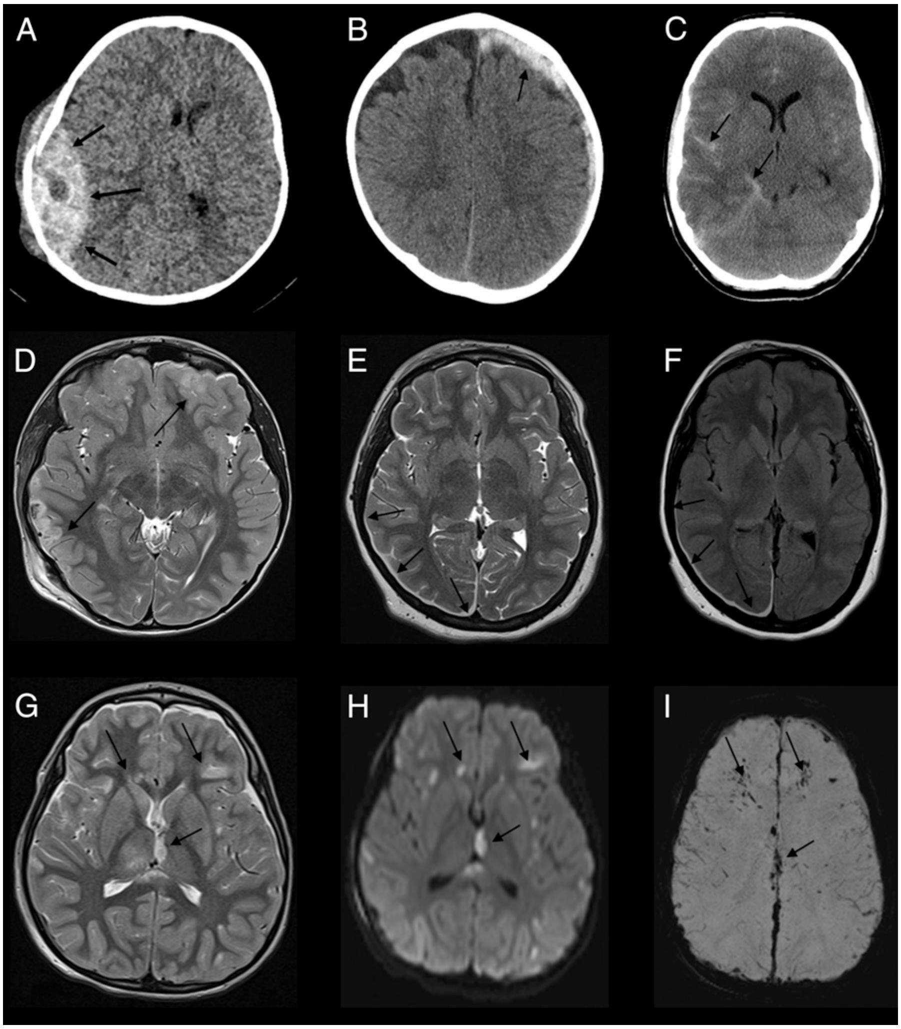

Figure 2. A. Computed tomographic (CT) scan, epidural hematoma, B. CT scan, subdural hematoma. C. CT scan, subarachnoid hemorrhage. D. Magnetic resonance image (MRI), T2, coup and contrecoup injury, example of contusion. E. and F. MRI T2 and fluid-attenuated inversion recovery, subdural hematoma (arrows). G-I. MRI T2, diffusion-weighted (DWI), and susceptibility-weighted (SWI) images, diffuse axonal injury (note the restricted diffusion on the DWI sequence and the areas of hemorrhage on the SWI sequence).

lesion. It is important to recognize that anisocoria caused by transtentorial herniation is almost always accompanied by loss of consciousness as a result of a compression of the midbrain (including the periaqueductal gray and other structures essential for maintaining consciousness).

Bilateral (Central) Herniation. If there is diffuse cerebral edema or a large bleed as a result of bilateral and severe cerebral injury, transtentorial herniation may be bilateral, resulting from a downward compression force (aka *central herniation*). In this case the patient will first develop decorticate posturing (arms flexed and legs extended) as a result of midbrain compression, and as the herniation worsens, decerebrate posturing (arms and legs extended) with extension downward of the compression (a simple mnemonic is to remember decorticate posturing is caused by injury above the red nucleus and with the arms flexed and pointing toward the cortex, while decerebrate posturing is generally caused by injury below the red nucleus and the arms are extended and pointing away from the cortex). The pupils will initially be dilated and reactive. As the syndrome progresses they will become fixed and upward eye movement will be compromised (resulting in a "sunsetting appearance").

Cingulate Herniation

Cingulate herniation (or subfalcine herniation) occurs as a result of the brain contents being displaced under the falx cerebri. This most often affects the frontal lobes as a result of a lateral rapidly growing mass lesion. The clinical signs of cingulate herniation are not as typical as those of the other herniation syndromes. Because the cingulate gyrus is compressed under the falx, the anterior cerebral artery may become compromised, with resultant ischemia of the medial motor

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TABLE 4. **Summary of the Major Herniation Syndromes and Clinical Manifestations**

HERNIATION	CLINICAL PRESENTATION	ASSOCIATED CEREBRAL PATHOLOGY
Cingulate	Symptoms secondary to anterior cerebral artery compression and stroke include contralateral foot paresis and numbness, abulia, and urinary incontinence. As the syndrome progresses, uncal herniation may occur.	Cerebral lateral compressive mass such as epidural or subdural bleed.
Uncal	Ipsilateral pupillary dilation (cranial nerve III), contralateral hemiparesis (cerebral peduncles). Note that the mass compressing the brain will often be contralateral to the herniation. Always associated with altered consciousness.	Cerebral lateral compressive mass such as epidural or subdural bleed compressing the cerebral peduncle against the tentorium toward the side opposite the mass (will result in a Kernohan notch).
Central	Initially bilateral fixed pupils, impaired upward eye movements (sunsetting appearance), decorticate followed by decerebrate posturing as the syndrome progresses.	Bilateral cerebral compressive mass such as diffuse TBI with associated edema and/or ischemia resulting in downward compression of the midbrain.
Tonsillar	Neck stiffness, cranial neuropathies, Cushing triad (hypertension, bradycardia, and irregular breathing).	Rare in the context of TBI, brainstem mass.

TBI=traumatic brain injury.

cortex, leading to weakness of the contralateral lower extremity. However, compression of the foramen of Monro will eventually lead to increased intracranial pressure, and the patient will develop symptoms typically associated with uncal herniation.

Tonsillar Herniation

Tonsillar herniation is the least common type of herniation seen in the context of TBI (because the brain stem is much less frequently involved in TBIs). Tonsillar herniation results from mass effect in the brain stem. As a result of the mass effect, the cerebral contents will shift downward, forcing the cerebellar tonsils and the medulla through the foramen magnum. Initially the patient may complain of neck stiffness. On examination cranial neuropathies may be evident. As the syndrome progresses the children will often develop the Cushing triad: hypertension, bradycardia, and slow and irregular breathing from compression of the medulla oblongata.

Evaluation of the Child with Moderate to Severe TBI

Evaluation of the child presenting with TBI depends largely on the initial assessment. The management will be radically different depending on whether the child arrives with an mTBI (GCS score >13) or a moderate or severe TBI as evidenced by a GCS score less than 13 (for further details on the management of the child with an mTBI refer to the Recognizing Concussion subsection). The child with a decreased level of consciousness should be rapidly evaluated for symptoms of herniation while ensuring that airway, breathing, and circulation measures are addressed. The history in this case needs to be gathered rapidly but remains essential. A description of the trauma, the presence or absence of seizure activity, evidence of loss of consciousness at the time of impact, or change in the level of consciousness will all help guide the management of these children. In addition, any child presenting with a decreased level of consciousness or complaining of neck pain should immediately undergo cervical spine injury precautions with immobilization of the spine. If the GCS score is less than 9 or if the child's mental status is fluctuating, an airway should be secured. The imaging modality of choice is CT because it is ideal to show both bone fractures and hemorrhage. However, DAI and contusion will not show as well on CT.

MRI versus CT

CT of the head is readily available in almost all emergency departments; it is a rapid study and is ideal to look for skull fractures or acute hemorrhages (acute hemorrhages will appear hyperdense on CT). In addition, if necessary, a CT of the C-spine can be added to evaluate for spinal fractures. The CT will also reveal areas of edema as evidenced by hypodense lesions, although these changes can take some time to become evident. It follows that a negative CT scan may require follow-up with MRI to fully characterize the lesion depending on the clinical presentation. However, CT is a poor study to evaluate for contusion or evidence of DAI. Furthermore, CT is associated with a significant amount of ionizing radiation. Note that the dose reduction techniques now commonly in use have resulted in significantly less dose exposure (refer to the Recognizing Concussion subsection for further discussion of imaging in mTBI).

MRI offers a better evaluation of hemorrhage. T1, T2, and T2 fluid-attenuated inversion recovery (FLAIR) series are

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best to evaluate for extra-axial hemorrhages. T1 and T2 sequences are also useful in dating the age of the hemorrhage. More subtle parenchymal injuries, shearing injuries, and microhemorrhage are better seen using susceptibility-weighted imaging. T2 FLAIR images are considered the most sensitive MRI sequences to look for subarachnoid hemorrhage, although CT is very sensitive for acute subarachnoid hemorrhage as well. Edema and ischemia are best evaluated with T2, FLAIR, diffusion-weighted imaging, and apparent diffusion coefficient sequences. In addition, diffusion- and susceptibility-weighted imaging will often reveal evidence of shearing injury or DAI that may have been missed on T1 or T2 sequences. Furthermore, MRI does not expose the children to ionizing radiation. However, MRI is time intensive and is not available in all hospitals 24 hours a day.

Management

In 2012, the second edition of the guide for the acute medical management of severe TBI in infants, children, and adolescents was published. (50) These guidelines were endorsed by multiple organizations, including the AAP, the Child Neurology Society, and the American Association of Neurological Surgeons. Although a detailed discussion of the management of the child with severe TBI is beyond the scope of this review, it is worth mentioning a few basic principles from these guidelines.

First and foremost, children with TBI are at very high risk for elevated intracranial pressure. This is especially notable in children with evidence of diffuse cerebral swelling on CT, a finding noted to be 75% specific for the presence of intracranial hypertension. Children with an altered level of consciousness are also at markedly increased risk for elevated intracranial pressure. These children need urgent management in an ICU setting.

Finally, a word must be said about the use of prophylactic antiepileptic medications. The guidelines cited previously herein note that the risk of posttraumatic seizures in the pediatric patient is approximately 10%. Based on a single study the guideline states that prophylaxis with phenytoin may be considered. However, although phenytoin and fosphenytoin remain the most commonly used antiepileptic medications in the prevention of posttraumatic seizures, there is accumulating evidence that levetiracetam is an excellent alternative. (51) Levetiracetam is available in an intravenous formulation, does not have a significant protein-bound fraction (as opposed to phenytoin that is 90% protein bound), has essentially no liver metabolism, and has very few significant drug interactions.

Special Considerations: Abusive Head Trauma

Inflicted TBIs have been labeled by a variety of different names, including nonaccidental trauma and shaken baby syndrome. In 2009, the AAP recommended replacing all of these terms with the nomenclature *abusive head trauma (AHT)*. (52) TBI inflicted on a child by an adult is unfortunately too frequent an occurrence. According to a recent CDC publication on AHT, it is the leading cause of head injury in infants. (53) Peak incidence occurs between the ages of 2 and 3 months, and AHT is rare after 2 years of age. The mortality and morbidity of AHT are considerable, with up to 20% of children succumbing to their injuries and two-thirds of the survivors having severe and permanent intellectual and physical impairments. The most common presentation of AHT is an infant or toddler with a decreased level of consciousness and/or seizures. Frequently in such situations there will be conflicting or vague histories from the parents or guardians. In addition, there may be a clear disconnect between the apparent severity of the injury and the described mechanism ("fell off a chair and hit his/her head on the floor" would be a very uncommon cause of TBI). One should also look for inappropriate affect in the adults accompanying the child. The evaluation of the child with suspected AHT should include an urgent CT scan of the head. Children with these types of injuries very frequently have a combination of subdural hemorrhages (54) and significant DIA (as evidenced by hypodense lesions on the CT scan). (55) In addition, skull fractures may be observed, but it is important to emphasize that the absence of skull fracture does not rule out AHT. Once there is suspicion of AHT and the child is clinically stable one should obtain a skeletal survey to look for evidence of new or old bone fractures elsewhere and a dilated funduscopic examination to look for evidence of retinal hemorrhages.

Of note, there are extremely rare metabolic disorders that are associated with spontaneous subdural hemorrhages. It is important to keep these conditions in mind when considering the differential diagnosis of AHT. These conditions include coagulation disorders, galactosemia, and glutaric aciduria. (56) Glutaric aciduria, galactosemia, and coagulation disorders can all be ruled out with relatively simple laboratory studies. Another condition to consider is Menke disease because it has been associated with spontaneous subdural hemorrhages. (57) However, this disorder should be evident based on the child's clinical appearance (severe developmental delay, epilepsy, and unusual and brittle appearance of the hair). One should also recognize that spontaneous subdural hemorrhages have been observed in children with benign extracerebral collections in infancy and minimal or no evidence of trauma. (58) Benign enlarged extracerebral spaces have been referred to by many names, including benign external hydrocephalus, benign communicating hydrocephalus, subdural hygroma, and others. It usually occurs in

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children with a head size larger than normal. The head size typically crosses the 98% growth curve until approximately 10 months of age and then stabilizes. These children are asymptomatic, and the condition is benign and typically resolves spontaneously.

CONCLUSION

TBI encompasses a broad spectrum of clinical presentations. These injuries represent a major challenge for the primary care physician because the prognosis varies from excellent, with complete resolution in a few days to a few weeks with mTBI, to catastrophic, with severe morbidity and mortality in the case of moderate to severe TBIs. However, a systematic approach to the child who experiences a TBI should help in the proper clinical management. Guidelines exist for the management of adult head injury (National Institute for Health and Care Excellence's Head Injury: Assessment and Early Management [https://www.nice.org.uk/guidance/cg176]).

These guidelines have been found to be highly reliable and easily adaptable to multiple environments, including low- and middle-income countries. (59) The CDC has now published guidelines for the diagnosis and management of mTBI in children. (10) The introduction and adoption of these guidelines will help resolve much of the guesswork that many primary care providers have to consider when evaluating children who have sustained some form of head trauma. (59)

Summary

- Traumatic brain injuries are the leading cause of death or severe disability in children older than 1 year, and the incidence is continuing to increase, making this topic especially relevant for the pediatrician.
- Based on a well-designed prospective cohort study, it is not recommended that all children presenting with head trauma obtain a head computed tomographic scan. (18) Rather, this decision should be based on the mechanism of injury and the signs and symptoms of the patient.
- Based on multiple cohort studies and expert opinion, concussion symptom checklists, such as the Child Sport Concussion Assessment Tool, the Postconcussion Symptom Scale, or the Graded Symptom Checklist, can be used to aid in concussion diagnosis and tracking symptom resolution in determining graduated return to play. (6)(11)(13)
- Children with moderate or severe traumatic brain injury are at high risk for elevated intracranial pressure; this is especially true of children presenting with altered consciousness. (50)
- Abusive head trauma is the leading cause of head injury in infants. The morbidity and mortality of abusive head trauma are considerable, with up to 20% of the infants succumbing to their injuries and two-thirds of the survivors having significant cognitive and/or physical impairments. (53)

Suggested Quality Improvement Project

With the increasing numbers of children presenting to emergency departments with TBIs, it is more important than ever that providers appropriately assess children to determine whether head CT is needed and to avoid unnecessary and harmful radiation exposure. Fortunately, there is a well-validated set of clinical criteria developed by the PECARN to assist in this decision-making process. (18) Previous efforts to implement these criteria in a community emergency department have resulted in a reduction in rates of head CT scan in children presenting with head trauma, (19) indicating that this is an excellent opportunity for further quality improvement projects.

Project: Reduction of head CT scan rates in children presenting with head injury.

Setting: Emergency department.

Prediction tool: PECARN prediction rule for clinically important TBIs.

Outcome Measure: Rate of pediatric head CTs in children presenting with TBI.

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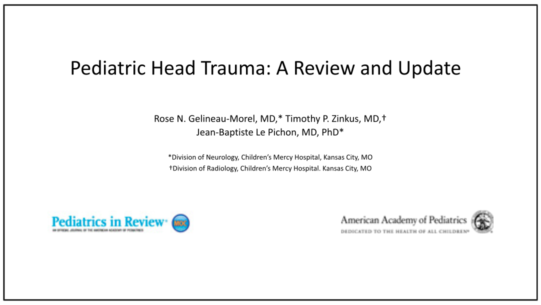

Pediatric Head Trauma: A Review and Update

Rose N. Gelineau-Morel, MD,* Timothy P. Zinkus, MD,†
Jean-Baptiste Le Pichon, MD, PhD*

*Division of Neurology, Children's Mercy Hospital, Kansas City, MO
†Division of Radiology, Children's Mercy Hospital. Kansas City, MO

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1. A 6-year-old girl is seen in the office after falling from her bicycle and striking her unhelmeted head yesterday. She did not lose consciousness at the time of injury, but ever since she has complained of headache and her mother feels that she is "not acting herself." An evaluation for the presumed diagnosis of mild traumatic brain injury, also known as concussion, is begun. Which one of the following is part of the COACH CV mnemonic for diagnosis of concussion?
   - A. Cardiovascular anomalies.
   - B. Head imaging normal.
   - C. Loss of Consciousness.
   - D. Orbital injury.
   - E. Vomiting.
2. You are participating as a sideline medical staff for an elite youth soccer team. A 14-year-old girl collided with another player and her head struck the other player's knee. She believes she lost consciousness for a few seconds, but she is verbally responsive when you evaluate her on the field. She complains of headache but is alert and oriented, with no neurologic deficits on your sideline physical examination. You pull her from the game, but she asks when she can return to her workouts. Which one of the following is the best guidance for the time she must be on complete rest, after which she can return to noncompetitive physical activity?
   - A. Immediate return to activity.
   - B. 2 days.
   - C. 5 days.
   - D. 7 days.
   - E. 10 days.
3. A 7-year-old boy is brought to the office for follow-up after he was seen in the emergency department for a concussion 1 week earlier. He was discharged with a standardized symptom assessment checklist, which his mother has been performing daily. His mother is concerned that he complains of headaches and seems "out of it" and short-tempered. She wants to know if this is going to be a prolonged recovery. Which one of the following is a risk factor for postconcussive syndrome?
   - A. Attention-deficit/hyperactivity disorder or learning disabilities.
   - B. History of supraventricular tachycardia.
   - C. Male sex.
   - D. Nonsport mechanism of injury.
   - E. Preadolescent age.
4. An 11-year-old boy is being seen for routine well-child care. His mother is concerned that he has had 2 concussions in early childhood and is reluctant about letting him participate in sports. Which one of the following sports would you advise her that he plays because of its lowest risk of concussion?
   - A. Biking.
   - B. Football.
   - C. Skiing.
   - D. Soccer.
   - E. Volleyball.

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5. A 14-year-old boy is being evaluated in the emergency department after a fall from a roof (approximately 20 feet). His vital signs include heart rate of 55 beats/min, respiratory rate of 29 breaths/min, and blood pressure of 140/90 mm Hg. He has a large laceration to the forehead and a bloody nose. He is minimally responsive, with occasional moans and no purposeful movement of his extremities. On secondary survey you note that the left pupil is larger than the right and poorly responsive. In addition, he has weakness of the left arm and leg. Which one of the following findings would be expected on head imaging given the clinical presentation?
    - A. Bilateral central herniation.
    - B. Cingulate herniation.
    - C. Diffuse axonal injury.
    - D. Tonsillar herniation.
    - E. Uncal herniation.

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Pediatric Head Trauma: A Review and Update

Rose N. Gelineau-Morel, Timothy P. Zinkus and Jean-Baptiste Le Pichon

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Index of Suspicion

1 Electrolyte Abnormalities in 7-day-old Girl

Inna Kaminecki, MD,* Thomas Vates, MD,* Frank Barrows, DO,*
Susan Hudome, MD*

*Department of Pediatrics, The Unterberg Children's Hospital at Monmouth Medical Center,
Long Branch, NJ

EDITOR'S NOTE

While many of our patients are excitedly back in school this month, others are struggling to adjust to educational programs for their special needs, and others are getting used to medication regimens and having access to emergency medications. This month's *Index of Suspicion* cases all touch on endocrinology, but they also remind us of our need to adapt school and medication administration to maximize outcomes for all of our patients.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A newborn girl was admitted to the NICU for prematurity and respiratory distress. The mother's pregnancy had been complicated with gestational diabetes and preeclampsia with severe hypertension. After administering 2 doses of betamethasone to the mother to promote fetal lung maturation before delivery, the infant was delivered vaginally at 34.1 weeks' gestational age after labor induction. The mother, a 49-year-old woman (gravida, 4; para, 2) had a significant obstetric history, including 1 miscarriage, 1 stillbirth, and 1 healthy child with another partner. The current partner and father of this newborn had 1 healthy child from a previous marriage.

The current patient was a product of in vitro fertilization performed outside of the United States with a donor egg and the father's sperm. Preimplantation genetic testing was performed to detect aneuploidy of chromosomes 13, 18, 21, X, and Y. Prenatal care was administered outside of the United States until 27 weeks' gestational age; thereafter, the mother received obstetric care in the United States. Fetal ultrasonography at 34 weeks' gestational age yielded normal results.

At birth, the patient's weight was 1,790 g. Initially she received respiratory support with nasal continuous positive airway pressure. A chest radiograph was consistent with surfactant deficiency. The APGAR scores were 4 and 8 at 5 and 10 minutes, respectively. Because the maternal group B streptococcal status was unknown, the patient underwent a limited laboratory evaluation for sepsis, and empirical antibiotic drug therapy was initiated. The initial laboratory evaluation revealed a normal complete blood cell count and negative blood culture. On physical examination the patient was noted to have a port-wine stain on her right

AUTHOR DISCLOSURE Drs Kaminecki, Vates, Barrows, and Hudome have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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flank. Significant findings noted on genital examination included a prominent clitoris and prominent labia minora.

On the second day after birth the patient's sodium level was 141 mEq/L (141 mmol/L); the potassium level was not reported due to sample hemolysis. On the seventh day, the patient presented with hyponatremia (sodium level, 127 mEq/L [127 mmol/L]), hyperkalemia (potassium level, 9.8 mEq/L [9.8 mmol/L]), and elevated creatinine (0.96 mg/dL [84 μmol/L]) and blood urea nitrogen (33 mg/dL [11.7 mmol/L]) levels. The elevated potassium level was attributed to sample hemolysis. The repeated potassium level was 10.2 mEq/L (10.2 mmol/L). The patient was also noted to have elevated calcium (13 mg/dL [3.2 mmol/L]) and phosphorus (8 mg/dL [2.5 mmol/L]) levels. An initial newborn screen for 57 diseases yielded normal results. Her blood sugar levels were stable, and her blood pressure and urine output were within the reference ranges. An electrocardiogram revealed PR and QRS intervals with normal durations and a normal T-wave amplitude. Nebulized albuterol and a single dose of kayexalate were initiated for hyperkalemia. Subsequent testing revealed the diagnosis.

DISCUSSION

After treatment with nebulized albuterol and kayexalate, repeated testing indicated a potassium level of 5.5 mEq/L (5.5 mmol/L) and a sodium level of 138 mEq/L (138 mmol/L). Physical examination and laboratory findings led to a suspicion of congenital adrenal hyperplasia (CAH). Pelvic ultrasonography revealed a normal uterus and left ovary, whereas the right ovary was not visualized; accordingly, karyotyping was ordered. Renal ultrasonography did not show any structural abnormalities. The patient was administered intravenous hydrocortisone and oral fludrocortisone for suspected CAH.

The results of blood testing indicated an elevated 17-hydroxyprogesterone level of 41,400 ng/dL (1252 nmol/L; reference range, 26–568 ng/dL [0.78-17 nmol/L]), elevated androstenedione level of 4,830 ng/dL (168 nmol/L; reference range, 50–449 ng/dL [1.7-15.6 nmol/L]), and elevated levels of 17-hydroxyprgenenolone and testosterone; the patient also had a low aldosterone level and an elevated renin level. Serum karyotyping yielded a normal female karyotype of 46, XX. The laboratory findings were consistent with a complete 21-hydroxylase deficiency. Her second routine newborn screening was positive for CAH. The patient's genetic testing detected a mutation in the *CYP21A2* gene and confirmed the diagnosis of CAH. The patient continued to receive intravenous hydrocortisone and oral fludrocortisone and was started on oral sodium chloride. A subsequent urologic evaluation identified a fused labia and vagina, with no obvious urethral opening noted on external examination. The patient's potassium level normalized to 5.1 mEq/L (5.1 mmol/L) on the third day after treatment initiation.

The Condition

CAH is among the most common inherited disorders, with an incidence of 1 per 15,000 live births. CAH is inherited in an autosomal recessive pattern, and more than 90% of such cases are caused by a 21-hydroxylase deficiency, the enzyme encoded by the *CYP21A2* gene. A 21-hydroxylase deficiency may present as the salt-wasting or simple virilizing form of classic CAH, or as "nonclassic" (late-onset) CAH. A 21-hydroxylase deficiency affects the conversion of 17-hydroxyprogesterone to 11-deoxycortisol, thus reducing the synthesis of cortisol and increasing the secretion level of corticotropin. Consequently, females exhibit increased production of androgens and virilization of the external genitalia. Although affected males appear normal at birth, scrotal hyperpigmentation and phallic enlargement may be observed. In addition, the salt-wasting form of CAH presents as an adrenal crisis, with hyponatremia, hyperkalemia, and failure to thrive.

Diagnosis

Routine newborn screening for CAH includes the measurement of 17-hydroxyprogesterone levels at 48 hours after birth, at which time most affected neonates have concentrations exceeding 3,500 ng/dL (105 nmol/L). However, screening for CAH is complicated by the fact that premature and low-birthweight newborns typically have higher 17-hydroxyprogesterone levels relative to full-term and normal-birthweight newborns. Given the potential risk of false-positive screening for CAH, the predictive value could be improved by adjusting the 17-hydroxyprogesterone cutoff values for both age and birthweight. Currently, 17-hydroxyprogesterone levels are adjusted only for the weight of the newborn in the state where our patient underwent screening.

The screening of premature newborns for CAH is further complicated by the administration of antenatal corticosteroid therapy for fetal lung maturation. Although a previous study found that long-term maternal corticosteroid treatment suppresses fetal 17-hydroxyprogesterone levels, the data regarding the effects of short-term maternal corticosteroid treatment on 17-hydroxyprogestrone levels remain limited. Therefore, a true-positive case of CAH may be missed because the potentially suppressive effects of corticosteroids can mask the relatively higher 17-hydroxyprogestrone level required for premature and low-birthweight

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infants to achieve a positive screening result. This might explain our patient's negative newborn screening result. A positive CAH result during neonatal screening should prompt repeated testing of the patient's 17-hydroxyprogesterone level. Although a cosyntropin stimulation test is considered the diagnostic gold standard, this test is not required. A high level of 17-hydroxyprogesterone is also considered diagnostic for CAH. Patients with classic 21-hydroxylase deficiency may also exhibit a mineralocorticoid deficiency. Importantly, a decreased aldosterone level will result in a low sodium level and an elevated potassium level, which can cause cardiac arrhythmia.

Management

The treatment of CAH requires a multidisciplinary team approach. A newborn with ambiguous genitalia and suspected CAH should be evaluated by an endocrinologist, geneticist, and urologist, In addition, the parents should be provided with psychosocial support. For the patient, hydrocortisone is administered with the intent to generate sufficient levels of glucocorticoids and, thus, resolve excessive corticotropin secretion and hyperandrogenemia. Furthermore, fludrocortisone therapy and sodium chloride supplementation will help maintain mineralocorticoid activity and manage electrolyte abnormalities. An adrenal crisis in a patient with CAH requires urgent medical treatment with a bolus of normal saline and a stress dose of hydrocortisone.

Responses to management for CAH should be evaluated by measuring the 17-hydroxyprogesterone and androstenedione levels, renin activity, blood pressure, and growth velocity. Both infants and children with CAH are at risk for disease-related complications, such as adrenal crisis, as well as complications associated with the use of glucocorticoids, such as a decreased linear growth velocity, osteoporosis, and obesity.

Patient Course

In this case, the patient's electrolyte levels stabilized during her hospital stay; before discharge, she presented with a potassium level of 5.0 mEq/L (5.0 mmol/L) and a sodium level of 139 mEq/L (139 mmol/L). She was subsequently discharged home on glucocorticoid replacement therapy with hydrocortisone and mineralocorticoid replacement with fludrocortisone and sodium chloride. At 14 months of age, the patient underwent surgical treatment including clitoroplasty and partial urogenital sinus mobilization vaginoplasty. Currently the patient is 19 months old and continues to take hormonal replacement therapy. Although the parents had received genetic counseling outside the United States before in vitro fertilization, they are not planning future pregnancies and, thus, did not receive further genetic counseling.

Lessons for the Clinician

- Girls with congenital adrenal hyperplasia (CAH) present with ambiguous genitalia, including clitoral enlargement and a common urethral-vaginal orifice. This condition may be difficult to diagnose in premature infants.
- Negative newborn screening does not exclude a diagnosis of CAH. Low-birthweight newborns and offspring of mothers treated with antenatal corticosteroids may receive false-negative screening results.
- The management of CAH includes lifelong glucocorticoid and mineralocorticoid replacement therapy. Females with a urogenital sinus may require reconstructive surgery.
- Couples often undergo in vitro fertilization procedures outside of the United States for various economic and social reasons; however, the quality standards for these procedures may not be as rigorous as those implemented in the United States. Clinicians should consider that some diseases are more prevalent in specific ethnic groups. For these reasons, a high index of suspicion should be maintained.

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Case 1: Electrolyte Abnormalities in 7-day-old Girl

Inna Kaminecki, Thomas Vates, Frank Barrows and Susan Hudome

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Index of Suspicion

2 New-Onset Seizure in a 5-year-old Boy with Autism Spectrum Disorder

Esha Shah, MD,* Ian Marshall, MD†

*Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ

†Department of Pediatrics, Rutgers-Robert Wood Johnson Medical School, Brunswick, NJ

PRESENTATION

A 5-year-old white boy with autism spectrum disorder (ASD) presents to the emergency department toward the end of summer after a generalized tonic-clonic seizure event witnessed by his parents at home. Physical examination reveals bilateral wrist widening and genu valgus without rachitic rosary, frontal bossing, or Harrison groove. Initial testing demonstrates very low levels of total serum calcium of 4.4 mg/dL (1.1 mmol/L) (reference range, 9.2–11.0 mg/dL [2.3–2.8 mmol/L]) and ionized calcium of 2.9 mg/dL (0.7 mmol/L) (reference range, 4.5–5.6 mg/dL [1.1–1.4 mmol/L]); the serum phosphorus level is slightly elevated at 5.6 mg/dL (1.8 mmol/L) (reference range, 2.5–4.5 mg/dL [0.8–1.5 mmol/L]), with alkaline phosphatase slightly elevated at 381 U/L (6.4 μkat/L) (reference range, 133–309 U/L [2.2–5.2 μkat/L]). Further testing reveals an unmeasurable level of 25-hydroxyvitamin D (25-OHD) at less than 5 ng/mL (<12.5 nmol/L) and an elevated intact parathyroid hormone level of 108 pg/mL (108 ng/L) (reference range, 15–65 pg/mL [15–65 ng/L]).

Left knee radiography (Fig) demonstrates widening of the growth plate with metaphyseal widening and fraying predominantly in the distal femur, abnormal lucency in the metaphysis of the bones, and diffuse osteopenia. An initial electrocardiogram shows corrected QT interval prolongation consistent with hypocalcemia.

Regarding his history, he had been formally diagnosed as having ASD at age 3 years. Diagnosis of his ASD was met with early interventions, including speech, physical, and occupational therapies. On further questioning his parents note that he had a history of food selectivity even before his formal ASD diagnosis but has not received specific feeding interventions. Despite his very limited diet, he does not receive any vitamin supplements. He is not taking medications that could interfere with vitamin D and/or calcium metabolism. He tends to remain indoors, with very limited sunlight exposure. Interestingly, despite his very limited diet, his growth chart shows his body mass index plotting above the 85th percentile for age and sex.

DISCUSSION

Patient Course

Nutritional assessment of his diet based on 24-hour recall—consisting of almost the same daily quantities of cookies, French fries, and water—indicated that he was receiving only 360 mg of calcium daily (the recommended dietary allowance

AUTHOR DISCLOSURE Drs Shah and Marshall have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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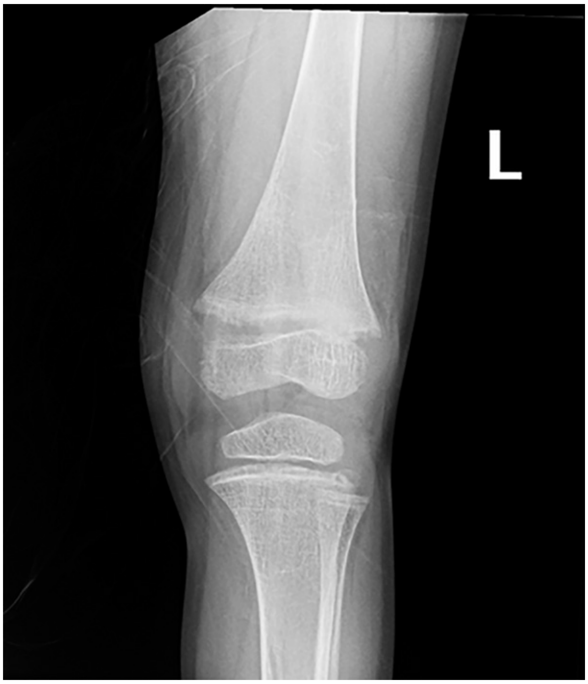

Figure. Left knee radiograph demonstrating growth plate widening, metaphyseal widening and fraying in the distal femur, abnormal lucency in metaphysis of bones, and diffuse osteopenia.

is 1,000 mg) and no vitamin D. He was diagnosed as having hypocalcemia with nutritional rickets due to severe calcium and vitamin D deficiency. Initial treatment with intravenous calcium normalized his serum calcium levels, with resolution of the electrocardiographic changes. Treatment was then switched to an oral calcium suspension providing 1,600 mg of elemental calcium daily. Oral vitamin D_3 therapy at 50,000 IU once weekly was started. Follow-up testing 2 days and 4 weeks after discharge showed normal total calcium levels at 9.4 mg/dL (2.4 mmol/L) and 10.1 mg/dL (2.4 mmol/L), respectively (reference range, 9.2–11.0 mg/dL [2.3–2.8 mmol/L]). He had also been referred to a feeding specialist while starting to receive a feeding intervention at school with a slight improvement in his diet.

The Condition

ASD is a complex developmental disorder characterized by varying degrees of impairment in 3 domains of functioning: communication, social behavior, and repetitive or stereotyped behaviors. (1) Recent reports of the incidence suggest that ASD occurs in approximately 1 in 68 children and is approximately 4.5 times more common in boys than in girls. (2) Children with ASD are more likely to demonstrate food selectivity (3) or picky eating, which is characterized by a restrictive repertoire of foods (4) due to avoidance of entire food groups, foods with a certain texture or a certain type, or solid foods.

Food selectivity and feeding problems are well described in children with ASD. (3)(5)(6)(7) A recent meta-analysis demonstrated that children with ASD were 5 times more likely to experience these issues than were children without ASD. (3) Unfortunately, these are often not detected by primary physicians during routine visits. This is partly due to lack of awareness to screen dietary habits in children with ASD. (3) In addition, exclusive use of the anthropometric parameters of height, weight, and body mass index often implies that these children with ASD are healthy due to consumption of sufficient calories to meet their energy requirements. (3)

Significantly lower serum 25-OHD levels have been demonstrated in children with ASD compared with control groups. (8)(9)(10)(11)(12) Possible explanations for differences in 25-OHD levels between these groups include lack of adequate sunlight exposure in children with ASD (13) due to less outdoor activity/more sedentary behavior, (14)(15) medications that interfere with vitamin D metabolism, (16) inflammation, (17)(18) and gastrointestinal issues. (19) Furthermore, a large proportion of children with ASD have lower vitamin D intakes than controls and do not meet their daily vitamin D requirements. (20)(21)(22)(23)

Another dietary factor that contributes to lower vitamin D and calcium levels is the adoption of the gluten-free, casein-free diet as an alternative therapy by many parents of children with ASD. (24) Gluten-free diets can eliminate cereals fortified with vitamin D, (25) and elimination of casein involves the avoidance of dairy products, which are also typically vitamin D fortified. (26) In addition, inadequate calcium intake contributes to lower calcium levels. (27)(28)(29)(30)

Although hypocalcemia as a result of nutritional rickets often presents as an asymptomatic laboratory finding, severe hypocalcemia can present as a life-threatening condition. Neuromuscular irritability, the hallmark of acute hypocalcemia, typically presents with numbness and tingling of the extremities and perioral region but in severe cases can result in bronchospasm and laryngospasm, (31) as well as seizures. (32) Cardiac electrophysiologic changes include prolongation of the QT interval due to lengthening of the ST segment. (33)

Although vitamin D deficiency is a main cause of nutritional rickets worldwide, in developing countries where calcium intake can be low, calcium deficiency itself is recognized as a major cause of nutritional rickets. (34) Historically, the main role of calcium deficiency in developed countries is to exacerbate the development of vitamin D–deficient rickets. (35) However, a single study in the United States by DeLucia et al (36) suggested that low

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dietary calcium intake alone was responsible for nutritional rickets in toddlers whose dairy intakes are limited.

Implications

Consequences of reduced vitamin D levels in children with ASD include a negative effect on bone mineralization. Neumeyer et al (21) reported lower bone mineral density in peripubertal boys with ASD compared with controls. The lower bone mineral density was hypothesized to be due to both impaired vitamin D status and lower exercise activity. (20)

Vitamin D deficiency can also result in nutritional rickets. This is characterized clinically by osseous signs and symptoms that include swelling of the wrists, knees, and ankles; leg deformities (genu varum or valgus); rachitic rosary (enlarged costochondral joints); Harrison grooves (horizontal grooves consisting of the depressions of the sixth and seventh costal cartilages due to constant tension at the site of the attachment of the anterior portion of the diaphragm); frontal bossing; and bone pain, restlessness, and irritability. (37) Radiologic features include splaying, fraying, cupping, and coarse trabecular pattern of metaphyses, widening of the growth plate, and osteopenia. (38) Only 2 case reports have been published of patients presenting with nutritional rickets secondary to food selectivity in ASD. (38)(39) Clark et al (38) reported an 8-year-old boy with ASD who presented with hypocalcemia and clinical and radiographic features of nutritional rickets due to vitamin D deficiency. This patient shared a very similar diet to our patient, consisting of French fries and water. (38) Stewart and Latif (39) reported a 15-year-old boy with ASD who also presented with nutritional rickets secondary to feeding difficulties. Supplementation of the diet with adequate vitamin D and other nutrients resulted in resolution of the rickets. (38)(39)

Lessons for the Clinician

- Careful screening by clinicians is essential for potential feeding issues, and accurate assessments should be considered of dietary intake of various essential nutrients to ensure that the recommended daily allowance for that specific age is met.
- Children with autism spectrum disorder may be at risk for poor nutrition because of their nontraditional eating habits.
- Dietary screening should complement anthropometric parameters of height, weight, and body mass index.
- Early intervention with nutritional and feeding therapies may be necessary in any child with autism spectrum disorder in whom feeding selectivity is appreciated.

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Case 2: New-Onset Seizure in a 5-year-old Boy with Autism Spectrum Disorder

Esha Shah and Ian Marshall

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3 Hypoglycemia in an Infant with Cholestasis

Nivedita Patni, MD,* Kathleen Collins, MD,[†] Perrin White, MD*

*Division of Pediatric Endocrinology, Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX

[†]Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, Stanford University, Palo Alto, CA

PRESENTATION

An 8-week-old boy presents with 2 days of worsening jaundice, lethargy, and poor feeding, without fever, vomiting, or diarrhea. At term he weighed 3,400 g (43rd percentile), had hypoglycemia on day 1, and received hyperbilirubinemia phototherapy for 5 days. Physical examination is noteworthy for a lethargic and jaundiced boy weighing 4,300 g (8th percentile). The liver edge is 4 cm below the costal margin. The phallus is 1.7 × 0.7 cm, with no hypospadias, normal scrotum, and descended testes.

Initial laboratory results are as follows: blood glucose, less than 20 mg/dL (<1.11 mmol/L); total/direct bilirubin, 17.8/13.5 mg/dL (304.4/230.9 μmol/L); alanine aminotransferase/aspartate aminotransferase, 258/686 U/L (4.31/11.46 μkat/L); free thyroxine, 0.96 ng/dL (12.4 pmol/L); and thyrotropin, 4.36 μIU/mL (4.36 mIU/L).

An intravenous glucose infusion is started, and the patient is admitted to the hospital. Liver ultrasonography reveals nonspecific coarse echogenicity with gallbladder wall thickening. Liver biopsy shows marked hepatocellular cholestasis, disarray and giant cell transformation, mild portal inflammation and portal fibrosis with early bridging fibrosis, and no abnormal storage material. Testing for herpes simplex virus types 1 and 2, enterovirus, Epstein-Barr virus, cytomegalovirus, adenovirus, human immunodeficiency virus, and hepatitis viruses is negative; levels of urine succinylacetone and organic acids are normal, as are plasma galactose-1-phosphate uridylyltransferase (GALT) and acylcarnitine levels. He is tested for *ATP8B1*, *ABCB11*, *ABCB4*, and *JAG1* mutations. Hypoglycemia continues despite an intravenous glucose infusion rate of 16 mg/kg per minute. After stopping his infusion for 30 minutes, the serum glucose level is 23 mg/dL (1.3 mmol/L). Concurrent laboratory results include insulin, 0.8 μIU/mL (5.6 pmol/L); β-hydroxybutyrate, 0.1 mmol/L; free fatty acids, 0.56 mg/dL (0.02 mmol/L); and growth hormone, 1.55 ng/mL (1.55 μg/L). A low-dose cosyntropin test and brain magnetic resonance imaging (MRI) (Figure) are performed.

DISCUSSION

Differential Diagnosis

Neonatal cholestasis can be caused by obstructed bile flow or functionally impaired hepatic bile secretion secondary to structural, infectious, genetic,

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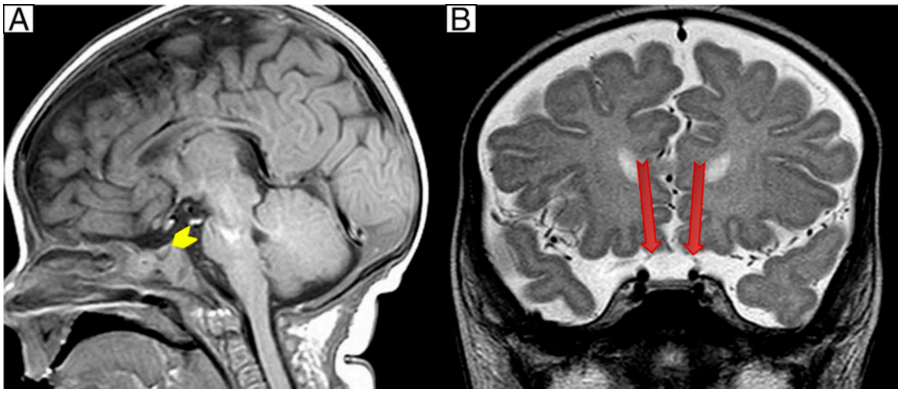

Figure. Brain magnetic resonance imaging. A. Sagittal T1-weighted image. The pituitary gland (yellow arrowhead) is diminutive in size and hypointense. A normal pituitary stalk is not visualized, indicating an ectopic neurohypophysis. B. Coronal T2-weighted image showing optic nerve hypoplasia (red arrows).

metabolic, or endocrine abnormalities. Biliary atresia is a fibro-obliterative disease of the extrahepatic biliary tree that presents with persistent jaundice, pale stools, and dark urine. Key diagnostic findings include ultrasonographic features of abnormal gallbladder size and shape, the "triangular cord" sign, poor gallbladder contractility, and absence of the common bile duct. Hepatobiliary scintigraphy shows lack of tracer excretion from liver to intestines, and liver biopsy demonstrates bile duct proliferation, a small cell infiltrate, portal fibrosis, and absence of sinusoidal fibrosis. (1)

Metabolic conditions such as galactosemia, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (fatty acid oxidation defects), and tyrosinemia type 1 can cause hypoglycemia along with cholestasis; these are usually detected by newborn screening in the United States. Galactosemia may present with vomiting and jaundice within a few days of milk ingestion. Hepatomegaly is often present, and *Escherichia coli* sepsis occurs frequently. Galactosemia is diagnosed by reduced activity of GALT. (2) Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency can present with hypoglycemia and liver disease along with elevated levels of long-chain acylcarnitines. (3) Tyrosinemia type 1, resulting from deficiency of fumaryl acetoacetate hydrolase, usually presents in infancy with severe liver dysfunction, growth failure, rickets, and renal tubular dysfunction. It is characterized by elevated tyrosine, methionine, and phenylalanine levels in plasma; increased succinylacetone levels in the blood and urine; and elevated tyrosine metabolite and δ-aminolevulinic acid levels in urine. Definitive diagnosis is made by measuring fumaryl acetoacetate hydrolyase activity in liver biopsy specimens or cultured fibroblasts. (4)

Progressive familial intrahepatic cholestasis is a group of rare autosomal recessive disorders presenting with intrahepatic cholestasis and features such as hearing loss, diarrhea, and growth failure, and it is caused by mutations in the *ATP8B1*, *ABCB11*, or *ABCB4* gene. (5) Alagille syndrome is an autosomal dominant disorder characterized by conjugated hyperbilirubinemia owing to bile duct paucity; vertebral anomalies; congenital cardiac defects, particularly pulmonary stenosis; ophthalmologic abnormalities such as posterior embryotoxon; and characteristic facial features. Heterozygous inactivating mutations in the *JAG1* gene are found in 94% to 96% of patients. (6)

Biliary atresia was ruled out by liver ultrasonography. A viral hepatitis panel was negative; normal urine succinylacetone and organic acid levels and plasma GALT and acylcarnitine levels ruled out metabolic diagnoses. There were no mutations in the *ATP8B1*, *ABCB11*, *ABCB4*, or *JAG1* genes.

Actual Diagnosis

The infant was diagnosed as having hypopituitarism.

The Condition

The brain MRI (Figure) showed a diminutive pituitary gland (yellow arrowhead), nonvisualization of the normal pituitary stalk, and an ectopic neurohypophysis. The optic chiasm and optic nerves were markedly diminutive (red arrows), and the olfactory bulbs were absent. The cortisol level increased from 1.3 μg/dL (36 nmol/L) to only 6 μg/dL (166 nmol/L) (reference range, >18 μg/dL [>497 nmol/L]) after low-dose cosyntropin stimulation.

Hypoglycemia is best evaluated with additional concurrent blood testing. Patients with hypopituitarism have low free fatty acid, lactate, insulin, cortisol, and growth hormone levels in the setting of hypoglycemia. Hypocortisolism can then be confirmed with a low-dose cosyntropin stimulation test. A brain MRI delineates anatomical causes of hypopituitarism.

A microphallus (ie, penile length <2.5 cm [7]), blunted growth hormone response to hypoglycemia, poor cortisol

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response to cosyntropin, and abnormal MRI findings confirmed the diagnosis of hypopituitarism owing to septo-optic dysplasia. Septo-optic dysplasia is a rare congenital syndrome defined by the presence of at least 2 of 3 features: 1) midline forebrain defects such as absence of septum pellucidum or corpus callosum, 2) optic nerve hypoplasia, and 3) hypopituitarism. (8) Hypopituitarism should be suspected in children with hypoglycemia and midline defects such as cleft palate, midface hypoplasia, hypertelorism or hypotelorism, or central incisor; optic nerve hypoplasia presenting with wandering nystagmus or poorly reactive pupils; and microphallus. Newborn boys with hypopituitarism usually have microphallus rather than ambiguous genitalia because in the first trimester, placental human chorionic gonadotropin stimulates testosterone secretion, which promotes differentiation of the external genitalia. Testosterone secretion and consequent penile growth after the first trimester depend on luteinizing hormone secreted by the fetal pituitary gland.

Cholestasis can rarely be a feature of hypopituitarism, (9) the mechanism of which remains unclear. (10) Cortisol modulates bile flow and bile acid synthesis (11); cortisol deficiency might affect hepatic transport of bile acids across bile canaliculi. Growth hormone plays an important role in bilirubin glucuronidation and modulates the biosynthesis and secretion of bile acid in rats (12); and growth hormone deficiency can lead to abnormal biliary cell and bile duct formation. (13) Untreated hypopituitarism has also been linked to congenital hepatic fibrosis. (14) Thyroxine deficiency (not present in this patient) delays maturation of hepatic UDP-glucuronosyltransferase activity and causes unconjugated hyperbilirubinemia. (15)

Patient Course

The patient was treated with hydrocortisone, growth hormone, and testosterone and was closely monitored for diabetes insipidus and hypothyroidism. The cholestasis resolved with growth hormone and hydrocortisone replacement.

Lessons for the Clinician

- Hypopituitarism should be suspected in children with hypoglycemia and midline defects such as cleft palate, midface hypoplasia, hypertelorism or hypotelorism, or central incisor; optic nerve hypoplasia presenting with wandering nystagmus or poorly reactive pupils; or microphallus.
- Cholestasis can be a rare presentation of hypopituitarism.
- Patients with hypoglycemia and conjugated hyperbilirubinemia should undergo endocrine evaluation for hypopituitarism.
- Cholestasis resolves with growth hormone and hydrocortisone replacement.

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Nivedita Patni, Kathleen Collins and Perrin White

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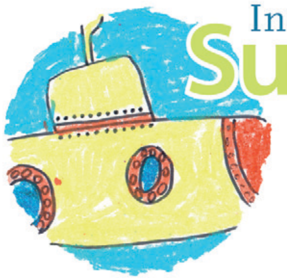

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4 Two Children with Presumed Inguinal Hernias

Jennifer Adair Williams, MD,* Gordon Bruce, MD,† Nishit Patel, MD,†
Jo-Ann Nesiama, MD, MS†

*Department of Pediatrics, Children's Health, Dallas, TX
†Department of Pediatric Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, TX

CASE PRESENTATIONS

We present 2 patients, A and B, with a similar condition.

Patient A is a 7-year-old girl with no medical history who is referred to the emergency department by her pediatrician due to concern for incarcerated inguinal hernia. She has a 3-day history of genital area redness, pain, swelling, and dysuria. She has had similar, although less severe, episodes of inguinal area swelling without redness twice in the past year, which resolved spontaneously. She denies fevers, vomiting, or dyspnea. Her vital signs are normal. She does not have any breast development or pubic hair, with a sexual maturity rating (SMR) of 1. Her physical examination reveals bilateral labial redness, tenderness with swelling extending to the suprapubic and bilateral inguinal area, and an enlarged clitoris with no vaginal opening (Fig 1). Findings from a complete blood cell count, comprehensive metabolic panel, and urinalysis are unremarkable. Pelvic ultrasonography shows cellulitis of the labia minora without discrete fluid collection or abscess, testicles in the bilateral inguinal canals, and no definite uterus or ovaries.

Patient B is an 11-year-old girl with no medical history who presents to the emergency department with a 4-day history of abdominal pain, fever, nausea, and vomiting concerning for appendicitis. Her vital signs are normal. Her examination reveals right lower quadrant abdominal tenderness. She has SMR 2 breasts, SMR 1 pubic hair, and normal external female genitalia. Her pediatric appendicitis score is intermediate, and ultrasonography of her appendix is inconclusive. A follow-up computed tomographic scan of her abdomen and pelvis shows appendicitis but also reveals an absent uterus and gonadal tissue in the right hemipelvis as well as a soft tissue mass in the left inguinal canal that appears more like a testicle than an ovary (Fig 2).

DISCUSSION

The Condition

Androgen insensitivity syndrome (AIS), a disorder of sexual development, is a syndrome whereby a genotypically XY individual is phenotypically female due to a resistance to the androgen hormones through a mutation in the androgen receptor. There can be complete or partial resistance, as demonstrated in the

AUTHOR DISCLOSURE Drs Williams, Bruce, Patel, and Nesiama have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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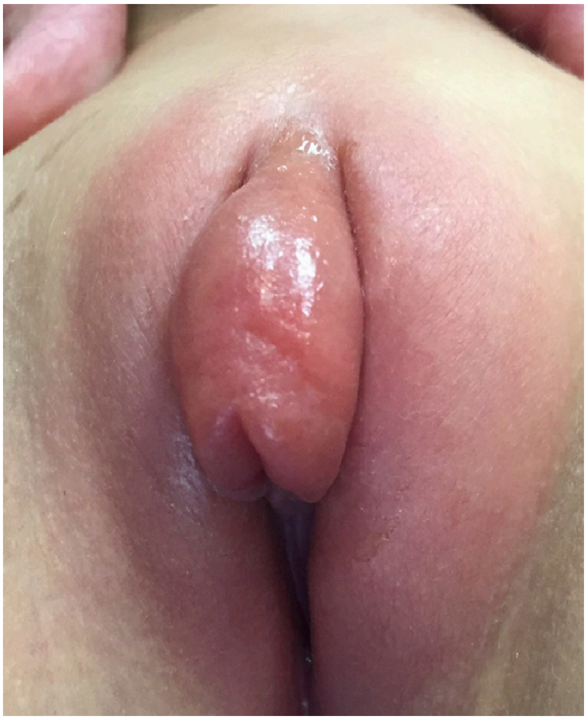

Figure 1. Physical examination findings for patient A.

cases presented. During embryotic development, the production of anti-Müllerian hormone (AMH) inhibits formation of the Müllerian ducts. These structures ultimately form the uterus, cervix, and proximal vagina. In AIS, AMH is present, but androgens secreted from the Leydig cells are not recognized and, therefore, no Wolffian ducts form to produce male genitalia. Because the innate tendency of human sexual development is female, the patient will develop external female genitalia. The syndrome may be first recognized with inguinal swelling in a phenotypic female, primary amenorrhea, or as a result of mismatch between prenatal sex prediction and the phenotype at birth. These patients go through puberty and develop estrogen through aromatization of the androgens. They enter puberty the same time as others and may be slightly taller, due to the growth-controlling region of the Y chromosome. There is a higher risk of gonadal tumors in AIS.

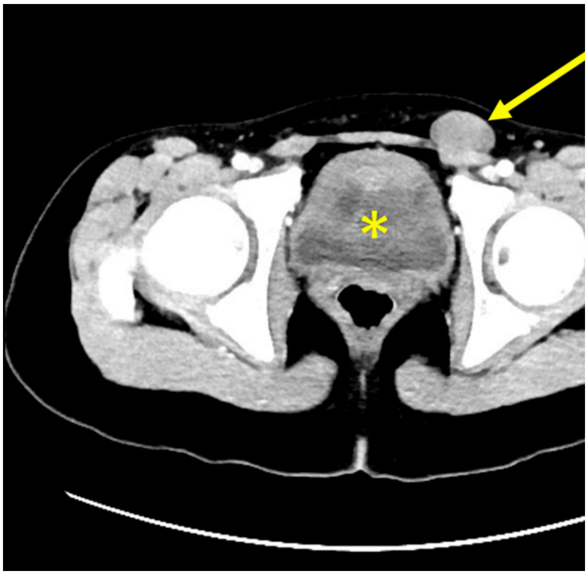

Figure 2. Computed tomographic scan of patient B with absent uterus (asterisk) and gonadal tissue in the left groin (arrow).

The pathogenesis of AIS is usually a missense mutation that encodes part of the androgen receptor. In complete AIS, the binding affinity is absent, whereas it is only altered in partial AIS. There are more than 800 mutations currently implicated in AIS. Whereas 30% of mutations are de novo, there is a X-linked inheritance pattern in complete AIS.

The differential diagnosis includes congenital adrenal hypoplasia, 5α-reductase deficiency, and 3β-hydroxysteroid dehydrogenase type 3.

Management

Management of AIS depends on the extent of the phenotype and should involve a multidisciplinary approach. Attention to various aspects, including functional, sexual, and psychological issues, should be undertaken. Furthermore, therapies such as gonadectomy, hormone replacement, and, in some cases, genitoplasty should also be discussed in accordance with the chosen sex and genetic advice.

Patient Courses

Patient A was given clindamycin for 10 days and was referred to the endocrinologist and gynecologist for further evaluation.

After extensive evaluation, she was diagnosed as having partial AIS. Her pertinent laboratory values include elevated testosterone of 126 ng/dL (4.4 nmol/L) (reference range, <10 ng/dL [<0.35 nmol/L]) and elevated AMH of 151 ng/mL (reference range, 0.53–7.78 ng/mL). The human chorionic gonadotropin stimulation test showed a normal testosterone to dihydrotestosterone ratio and a normal testosterone to androstenedione ratio. Fluorescence in situ hybridization and chromosomal microarray analysis showed 46, XY karyotype. No specific androgen receptor mutations were found on an androgen insensitivity panel. Of note, a physical examination revealing no vaginal opening in this patient during a previous visit to her pediatrician should have prompted earlier referral for evaluation.

She underwent a bilateral inguinal hernia repair, bilateral orchiectomy, and vaginoscopy with vaginal calibration. A pathology specimen showed no evidence of Leydig cell hyperplasia. She will undergo induction of puberty at approximately 10 years of age and be raised as a girl.

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Patient B was given metronidazole and ceftriaxone for her appendicitis. During the laparoscopic appendectomy, a testiculoform right gonad was found, and she had a left gonad measuring 2×3 cm that was fixed in the inguinal canal. She also had bilateral inguinal hernia. No uterus was identified. A vaginal examination was performed under anesthesia and revealed a vagina measuring 5 to 6 cm with no palpable cervix.

She was diagnosed as having complete AIS. Her pertinent laboratory findings included karyotype 46, XY and an elevated testosterone level of 136 ng/dL (4.7 nmol/L). The family also plans for her gonads to be removed with estrogen therapy during puberty. This patient will not need vaginal dilation given the initial measurements of her vagina. She will also be raised as a girl.

Lessons for the Clinician

- Always complete a thorough external genital examination in any child with lower abdominal pain or inguinal area swelling.
- Androgen insensitivity syndrome (AIS) should be included in the differential diagnosis for a girl with inguinal area swelling or primary amenorrhea.
- Management of AIS should be undertaken by a multidisciplinary team.
- Gonadectomy is recommended because of the small risk of gonadal tumors.

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Case 4: Two Children with Presumed Inguinal Hernias

Jennifer Adair Williams, Gordon Bruce, Nishit Patel and Jo-Ann Nesiama

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Case 4: Two Children with Presumed Inguinal Hernias

Jennifer Adair Williams, Gordon Bruce, Nishit Patel and Jo-Ann Nesiama
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Neonatal Brachial Plexus Injury

Morgen Govindan, MD,* Heather L. Burrows, MD, PhD*
*Department of Pediatrics and Communicable Diseases, Mott Children's Hospital, University of Michigan Medical School, Ann Arbor, MI

Neonatal brachial plexus injury presents as weakness or paralysis of the upper extremity or extremities at birth, most often related to stretching of the brachial plexus in the perinatal period. Early recognition and management in the newborn period can significantly impact outcomes. Therefore, it is important for pediatricians to be knowledgeable regarding the clinical spectrum of injury, prognosis, and treatment options.

The incidence of brachial plexus injury ranges from 0.4 to 4 per 1,000 births. The primary risk factors are shoulder dystocia and macrosomia (birthweight >4,000 g). Other risk factors include maternal diabetes or obesity, prolonged labor, and delivery with forceps or a vacuum extractor. Although cesarean delivery decreases the risk of brachial plexus injury, it does not eliminate it, and it carries other risks for both mother and infant.

The brachial plexus is composed of nerve roots C5 through T1 and can be divided into the upper (C5 and C6), middle (C7), and lower (C8 and T1) trunks. Peripheral nerves arising from the plexus innervate the muscles of the upper extremity. There are multiple ways to classify brachial plexus injuries. One example uses the Narakas classification system, which grades the severity of injury from group I to IV, with lower groups being associated with higher rates of spontaneous recovery. Group I represents injury to the upper trunk alone, C5 and C6. The shoulder is adducted and internally rotated with an extended elbow, commonly described as the "waiter's tip" position known as Erb-Duchenne palsy. Function of the wrist and hand is maintained, with normal grasp. Group I is the most common type of injury, accounting for approximately 50% of cases, and has the best prognosis, with full spontaneous recovery in up to 90% of patients. Group II, or extended Erb palsy, is related to injury of the C5, C6, and C7 nerve roots and has an intermediate prognosis with an approximate 65% rate of spontaneous recovery. Group II presents similarly to group I with the addition of weakness in the wrist extensors. In groups III and IV, injury is to the entire plexus (roots C5, C6, C7, C8, and T1), which manifests as weakness or paralysis of all the muscles of the arm. The arm remains in neutral position with minimal movement. Group IV is distinguished from group III by the presence of ipsilateral Horner syndrome (miosis, ptosis, and anhidrosis), consistent with injury to the sympathetic chain. This suggests an avulsion injury, and spontaneous recovery is unlikely to occur. Isolated injury to the lower trunk (roots C8 and T1), described as Klumpke palsy, is rare and accounts for less than 2% of patients.

The severity of nerve damage ranges from a stretch injury, in which there is no permanent damage to the nerve, to root avulsion. In a stretch injury, also referred to as neurapraxia, the resulting conduction block recovers fully after hours to weeks. This is the most common type of injury in brachial plexus palsy. Nerve rupture is a more severe form of injury, with limited recovery related to scar tissue that forms into a neuroma and blocks axon regeneration. The most severe type of

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Neonatal Brachial Plexus Palsy—Management and Prognostic Factors. Yang LJ-S. *Semin Perinatol.* 2014;38(4):222–234

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injury is root avulsion, with no spontaneous recovery, and surgery will be required.

Brachial plexus injuries are diagnosed clinically on the basis of the history and physical examination findings. A brachial plexus injury may be suspected in an infant with asymmetrical arm movement or Moro reflex. Maternal and birth histories are important for identifying risk factors for injury. Providers should complete a detailed musculoskeletal and neurologic assessment, including both passive and active range of motion and assessment of normal reflexes. Physical examinations in the neonatal period should include evaluation for a bony injury, as a fracture to the clavicle or humerus can present similarly to a brachial plexus injury due to pain limiting range of motion. Respiratory status and symmetry of chest movements should also be assessed because the phrenic nerve (composed of nerves C3, C4, and C5) can be involved in more proximal brachial plexus injuries. When concerns are noted on physical examination, a chest radiograph should be obtained to assess for clavicular or humeral fracture, as well as for the presence of diaphragmatic paralysis. Several findings on clinical examination can be suggestive of an avulsion injury, including the presence of Horner syndrome, hemidiaphragm paralysis from phrenic nerve injury, and winging of the scapula, which indicates an injury to the long thoracic nerve.

When an avulsion injury is suspected, advanced imaging can be helpful for diagnostic purposes as well as for potential surgical planning. Computed tomography myelography has previously been the preferred modality for evaluating for nerve root avulsion. However, it requires general anesthesia and lumbar puncture to introduce the intrathecal contrast, and it exposes the infant to ionizing radiation. As a result, magnetic resonance imaging (MRI) is now the preferred modality over computed tomography myelography because MRI can provide similar information without the risks of lumbar puncture or ionizing radiation. In addition, MRI can often be performed with minimal or no sedation in infants.

Management with physical and/or occupational therapy should begin as early as possible. Goals of rehabilitation include maintaining range of motion to prevent the formation of contractures or joint deformity. Caregivers should be taught how to perform passive stretching at home to maximize the effectiveness of therapy. Parents should also be encouraged to provide "tummy time" multiple times throughout the day to prevent plagiocephaly because torticollis has been associated with brachial plexus injury. Motor training can help promote normal development and prevent compensatory movements. Immobilization of the affected limb is not recommended in the absence of a bony fracture.

Close follow-up with serial examinations is critical in the management of brachial plexus injuries. In addition to the type and severity of the lesion, the speed of recovery factors significantly into overall prognosis. Biceps muscle strength testing is one of the simplest and most reliable measures of recovery. When an infant regains biceps strength within the first month, complete recovery is expected. If, on the other hand, biceps strength has not been recovered by 3 months, surgical repair should be considered. There remains some controversy regarding the ideal timing of surgery. However, surgery is generally recommended between 3 and 6 months for the most severe injuries because early surgery minimizes motor end plate loss.

Although most infants with brachial plexus injury recover fully, recent studies report residual deficit in up to 20% to 30% of cases, more commonly in higher grades of injury. Because approximately 5,000 brachial plexus injuries occur annually, pediatricians are likely to encounter this disorder in their practice. Because of the complexity of brachial plexus injury and the potential long-term ramifications, it is crucial to educate families appropriately regarding the clinical presentation, prognosis, and treatment options. Families may have significant emotional responses and are at risk for psychological distress. Many interdisciplinary clinics include social workers and/or psychologists and can provide comprehensive care for affected families. Infants should be referred early to an interdisciplinary clinic specializing in brachial plexus injuries.

COMMENT: Brachial plexus injuries were first reported by William Smellie in 1764. Conservative treatment was the prescribed approach until the end of the 1960s, when research revealed the importance of the distinction between the different types of injury and future potential morbidity. The important clinical dilemma for pediatricians is to distinguish those injuries for which there is a high likelihood of spontaneous resolution, such as neurapraxia, and the approach to do no harm, while balancing with those injuries where surgical intervention is critical for quality of life measures, such as with nerve root avulsions. Add to this, some of the challenges of physical examinations in young neonates and the inability to have voluntary cooperation from the patient. Hence, the recommendation stated in this *In Brief*

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of periodic and longitudinal examinations in the first weeks and months of life is critical. Enlisting the support of a multidisciplinary team consisting of a neurologist, a neurosurgeon, an orthopedist, physical and occupational therapists, and social workers is needed in more severe cases. The goal is for preservation of function of the hand grasp, in addition to elbow and shoulder mobility and function. Ongoing research is critical to better delineate best treatment strategies and the timing to enhance function and quality of life.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

Correction

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Sudden Cardiac Death: A Pediatrician’s Role: 1. C; 2. B; 3. E; 4. C; 5. D.
Pediatric Head Trauma: A Review and Update: 1. A; 2. B; 3. A; 4. E; 5. E.

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Visual Diagnosis

Rapidly Progressing Oral Ulcer in a 13-year-old Girl

B. Jason Brotherton, MD, MS*

*Department of Internal Medicine and Pediatrics, PCEA Chogoria Mission Hospital, Chogoria, Kenya

PRESENTATION

A 13-year-old girl presents to our mission hospital in rural Kenya with a 2-week history of a rapidly progressing painless ulcer on her jaw and inside the oral cavity. There has been no fever or weight loss, but she reports some intermittent night sweats. She denies any oral trauma or recent dental procedures. She and her mother deny previous admissions to the hospital. No other members of her family have had a similar lesion. She and her family live 4 hours away, in an arid region of the country. Before presentation, they tried no treatments for this illness.

Physical examination is significant for a thin, pleasant girl. Vital signs on admission are temperature of 97.7°F (36.5°C), respiratory rate of 16 breaths/min, and heart rate of 94 beats/min. There is a 2 × 2.5–cm necrotic eschar overlying her mandible just below her lip with surrounding swelling (Fig 1). Internal oral examination is limited by her inability to fully open her mouth. Pertinent findings are halitosis, a linear groove with yellow tissue, and further necrosis beneath the external lesion (Fig 2). Her dentition appears normal. The linear groove progresses above the inferior alveolar ridge and extends posteriorly along the buccal mucosa. The tongue and the hard and soft palate are not involved. Her submandibular glands are easily palpable on the left, but there are no cervical or supraclavicular lymph nodes appreciated. The remainder of her physical examination is unremarkable except for a BMI of 13.4 (<3rd percentile).

Laboratory investigations include a complete blood cell count significant only for a low normal hemoglobin level of 12.8 g/dL (128 g/L), a normal basic metabolic panel, and negative results for human immunodeficiency virus (HIV) serology and cartridge-based nucleic acid amplification test of expectorated sputum for tuberculosis (TB). A peripheral smear does not show any malarial parasites. Based on risk factors and clinical presentation, the diagnosis is made.

DIAGNOSIS

There are several etiologies to consider for a rapidly progressing skin lesion. Leprosy, caused by *Mycobacterium leprae*, typically presents as a chronic wound associated with preceding numbness and paresthesia. The affected areas of skin are often hypopigmented.

Ecthyma gangrenosum commonly begin as a painless lesion that, over several hours, progresses to form gangrenous ulcers. These lesions are commonly due to pseudomonal bloodstream infections occurring in immunocompromised hosts.

AUTHOR DISCLOSURE Dr Brotherton has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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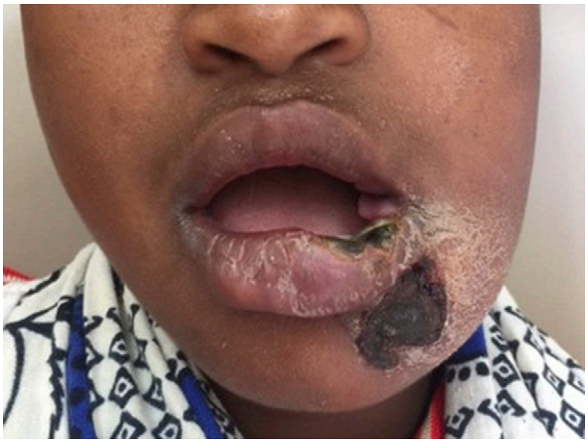

Figure 1. Anterior view of mandibular eschar and edema taken on the day of hospital admission.

Although these infections can occur anywhere, the most common locations are the genital and gluteal areas.

Mucosal leishmaniasis is a devastatingly destructive chronic manifestation of a primary cutaneous *Leishmania* infection. These can occur up to 10 years after a primary event. The mucosal variant of leishmaniasis is painful and can occur anywhere from the nasal cavity down to the vocal cords, resulting in a spectrum of symptoms from nasal congestion to respiratory distress.

Cervicofacial necrotizing fasciitis is an aggressive, rapidly spreading infection along fascial lines. This occurs most often after a dental procedure or oral trauma. As with most instances of necrotizing fasciitis, this too is extremely painful. These lesions have typically been described in adults with HIV.

Noma, or cancrum oris, is a rapidly spreading infection occurring commonly in malnourished children living in sub-Saharan Africa. It classically begins as a painless oral ulcer and spreads quickly, causing soft tissue edema with a well-demarcated area of black necrosis.

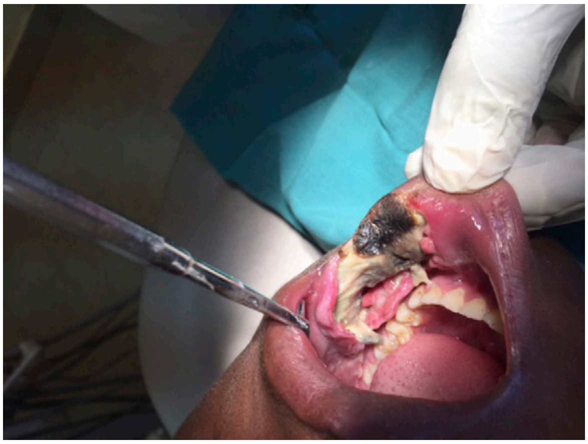

Figure 2. Internal view of a necrotizing mucosal lesion extending along the buccal mucosa to the posterior oral cavity.

Given our location, the patient's environmental risk factors, and the appearance of the lesion, our diagnosis was noma.

DISCUSSION

Noma, or cancrum oris, is a gangrenous infection of the oral cavity that rapidly expands to involve the overlying skin and deep bony structures. The disease has a long history, with Hippocrates describing cases in the 5th century BC. Without recognition and treatment, the mortality rate is exceedingly high. Noma is a disease of extreme poverty and at one time was prevalent in the United States and Europe. Today it is concentrated in the "noma belt," which consists of much of sub-Saharan Africa.

Additional risk factors include malnutrition, absence of breastfeeding, poor sanitation, recent measles infection, malaria, concomitant HIV or TB infection, poor oral hygiene, and proximity to livestock. (1) The peak season for cases in sub-Saharan Africa include the dry season, when food insecurity is highest.

The pathophysiology of noma is not fully understood but it is believed to be multifactorial in origin. In nearly all instances, the baseline patient characteristic is malnutrition. This has a direct effect on the immune system's ability to fight infection and wound healing. Malnutrition can be the result of food insecurity or chronic infections such as HIV and TB. In addition, both of these infections can render the body's immune system less effective at mounting a response to other invading organisms. Extreme poverty lends itself to creating an environment with destitute living conditions and suboptimal dental hygiene practices. Lack of proper sanitation increases exposure to multiple pathogens. Poor dental hygiene allows for overgrowth of oral bacteria. Proximity to livestock, in the setting of poor living conditions, again increases the organismal exposure. These risk factors, coupled with the weakened immune system, create a vicious cycle of breaking down the mucosal and gingival integrity, leading to chronic infection and subsequent necrosis. (2)

Noma typically begins as a small ulcer inside the mouth that can rapidly expand. As the lesion expands and becomes necrotic, fever, lymphadenopathy, and halitosis are common findings. At this point in noma development, there can be significant edema of the surrounding and underlying tissues. If left untreated, the infection extends to deep tissues, ultimately making its way to the bony structures underneath, leaving a trail of skin and mucosal necrosis behind.

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Responsible bacteria include oral flora such as *Fusobacterium necrophorum*, *Capnocytophagia pyogenes*, *Prevotella intermedia*, and *Bacteroides fragilis*. (3) These may become pathologic in the setting of immune suppression by the factors outlined previously herein.

Before the treatment with antibiotics and nutritional rehabilitation, the mortality rate ranged from 70% to 90%. Many countries do not keep exact mortality data for cases of noma, but some studies have shown that using antibiotics has decreased mortality to 15%. (4)

Current treatment strategies focus on combating the infection with antibiotics, correcting electrolyte and fluid abnormalities, treating underlying conditions (ie, HIV, TB, malaria), and improving nutrition. Common antibiotic regimens include a penicillin (amoxicillin, amoxicillin–clavulanic acid, or benzylpenicillin) coupled with an anaerobic agent such as metronidazole. Chlorhexidine digluconate (0.12%–20%) has also been used as a daily mouth wash to clean the oral cavity.

Surgical intervention has been used for wound debridement, return of function by release of trismus, and, in many cases, reconstruction of devastated tissues. The timing of such interventions varies. After debridement, skin flaps can be transferred from other sites on the body. Wound care is critically important with frequent dressing changes soaked in antiseptic.

Historically, the primary complication was death. Now the main complications include facial disfigurement, oral trismus, early tooth loss, fibrous ankylosis of the temporomandibular joint, and hypoplasia of the maxilla and mandible. (3) Because of frequent and severe complications of facial disfigurement, noma survivors should be counseled and followed to address any emotional and social effects of surviving the disease.

PATIENT COURSE

Our young patient was admitted to the hospital and started on intravenous benzylpenicillin and metronidazole. A further evaluation was undertaken to evaluate for underlying infections or malignancy that may be contributing to the onset of noma.

A peripheral blood smear showed no evidence of blast cells. Blood and urine cultures were negative. It was concluded that her risk factor was severe malnutrition.

She was evaluated by our surgical team and nutritionist. After stabilization and several days of antibiotic drug therapy, she was taken to the operating room for surgical debridement of the lesions and removal of the eschars. Surgical intervention was pursued early due to the concern that she would be lost to follow-up due to the distance traveled to reach our facility. She remained hospitalized for 2 weeks, undergoing additional nutritional rehabilitation and counseling.

She returned 1 month later for a second debridement and placement of an Estlander flap.

Summary

- Noma is an underrecognized and undertreated necrotizing infection of the face and oral cavity that can be extremely disfiguring or deadly.
- Early recognition and treatment with antibiotics and aggressive nutrition rehabilitation improves outcomes.
- Common treatment regimens include a penicillin (amoxicillin, amoxicillin–clavulanic acid, or benzylpenicillin) and an anaerobic agent (metronidazole).
- Surgical intervention is primarily for debridement, restoration of function, and cosmetic purposes. However, many facilities in low- and middle-income countries lack this expertise.
- In addition to the medical aspects of noma, it is important to address the social and emotional issues of this disfiguring disease.

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Cold Weather Viruses

Asif Noor, MD,* Theresa Fiorito, MD,* Leonard R. Krilov, MD*†

*Department of Pediatrics, Children's Medical Center, NYU Winthrop Hospital, Mineola, NY
†Department of Pediatrics, State University of New York, Stony Brook School of Medicine, Stony Brook, NY

Education Gap

Clinicians must learn to identify viral infections in children during the winter months and must practice caution with the use of unnecessary medications in such cases. Recognition of the clinical pattern of viral infection (eg, bronchiolitis) in conjunction with judicious use of viral tests (either office-based immunoassays or newer molecular tests) may assist in epidemiological monitoring, cohorting patients in the hospital, withholding unnecessary therapies, and providing a definitive diagnosis.

Objectives

After completing this article, readers should be able to:

1. Review the epidemiological aspects and clinical signs and symptoms of common cold weather viruses.
2. Recognize situations in which viral testing is indicated.
3. Recognize situations in which treatment is indicated.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
Adv	adenovirus
CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration
hMPV	human metapneumovirus
PCR	polymerase chain reaction
PIV	parainfluenza virus
RSV	respiratory syncytial virus
RV	rhinovirus

CASE

In early November you are evaluating a 9-month-old boy born at 33 weeks of gestation. The infant presents with 2 days of fevers (101°F–102°F [38.3°C–38.8°C]), copious rhinorrhea, and 1 day of coughing with difficulty breathing. He is otherwise feeding well and has had adequate urination. His 4-year-older sister has an upper respiratory tract infection.

On physical examination, the infant has a respiratory rate of 45 breaths/min without chest wall retractions. On auscultation there is good air entry with scattered rhonchi bilaterally. What is the most appropriate next step in management?

a. Obtain respiratory syncytial virus (RSV) and influenza antigen testing.
b. Obtain a chest radiograph to look for focal infiltrate.
c. Provide supportive care with nasal suctioning, fever control, and attention to adequate fluid intake.
d. Perform a trial of nebulized albuterol in the office.

This case represents a common scenario encountered by pediatricians during the winter months in the United States. The winter season in the Northern hemisphere begins in late December and ends in late March. An increase in the number of viruses causing infections begins 1 to 2 months before and continues

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for several weeks to months after the winter season. The reasons why cold weather is associated with a rise in viral infections is likely due a longer time spent indoors, the ability of certain viruses such as influenza to survive in cold temperatures, and low humidity. (1)

The infant in the previously described case has clinical bronchiolitis. The latest clinical practice guidelines (2) from the American Academy of Pediatrics (AAP) from 2014 recommend supportive care in patients with viral bronchiolitis [correct answer: c]. RSV is the most common cause and is responsible for 80% of bronchiolitis-associated hospitalizations in children. (3) Other cold weather viruses, such as influenza, parainfluenza virus (PIV) type 3, human metapneumovirus (hMPV), adenovirus (Adv), and rhinovirus (RV), also cause bronchiolitis illness. It is hard to distinguish RSV bronchiolitis from other causes of viral bronchiolitis based solely on history or physical examination findings.

The clinical practice guidelines do not recommend routine testing for viral bronchiolitis because it does not change management for the individual patient. However, the advent of newer multiplex polymerase chain reaction (PCR) assays can assist with a definitive diagnosis. Specific diagnosis can help in cohorting hospitalized children and provides objective data to limit the use of unnecessary medications. Chest radiographs are not routinely recommended because the presence of infiltrates does not correlate with disease severity or bacterial superinfection.

In this article we provide a review of common respiratory viral infections seen in the cold weather months. RSV and influenza account for most of these infections during the winter months and cause annual outbreaks from late fall to early spring. This review also includes other important viruses responsible for respiratory infection in children, ie, PIV (peak in fall and spring), hMPV (peak in late winter and fall but activity is seen throughout the year), respiratory Adv (throughout the year), and RVs (year-round, with increased prevalence from September through May) (Fig).

RESPIRATORY SYNCYTIAL VIRUS

Introduction

RSV is the most common cause of annual winter outbreaks of lower respiratory tract disease in infants and young children. Worldwide RSV is responsible for an estimated 3.4 million hospitalizations annually in children younger than 5 years. (4) Every year in the United States on average approximately 57,000 RSV-associated hospitalizations occur in children younger than 5 years, and the annual costs are approximately $2.6 billion. (5)(6) Prematurity in infants, underlying chronic lung disease, and heart disease are risk factors for severe RSV infection in children; however, the largest number of RSV hospitalizations occur in healthy infants. The estimated RSV pneumonia-related mortality in the United States is 3.1 per 100,000 person-years in children younger than 1 year. (7)

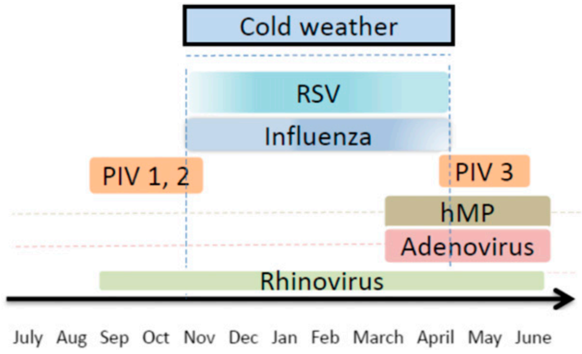

Figure. Duration of activity of common cold weather viruses. Respiratory syncytial virus (RSV) and influenza activity are seen only in the winter months; parainfluenza virus (PIV) types 1 and 2 are seen in fall and PIV-3 in spring; human metapneumovirus (hMPV) infections are seen throughout the year but peak in later winter and spring; and adenovirus is seen throughout the year, but epidemic respiratory adenovirus may occur in later winter and spring.

Epidemiological Profile. RSV infection is primarily seen in the winter months throughout the United States except in Florida, where it extends throughout much of the year. Nationally, onset of the RSV season ranges from mid-September to mid-November, peaks from mid-December to mid-February, and the season offset occurs mid-April to mid-May. In tropical climates, peak RSV activity correlates with the rainy season. (8) RSV circulation also seems to differ for Hawaii based on limited data. An insufficient number of laboratories in Hawaii report RSV antigen and RSV PCR results to the National Respiratory and Enteric Virus Surveillance System, but RSV activity seems to be present throughout the year. In Texas, RSV activity begins typically in September or October and peaks in December or January.

Transmission. RSV is transmitted primarily via inoculation of nasopharyngeal mucosa or conjunctiva through direct contact with viral-containing secretions, fomites, or droplets. RSV can survive 4 hours on hands and fomites.

RSV spreads effectively through exposed family members. In a prospective study of families with an infant and older siblings, 44% of the families became infected with RSV within 3 months, and in almost all cases an older sibling (2–16 years old) introduced the virus into the family. (9) The incubation period is 2 to 8 days (Table).

Clinical Features

Primary Infection. Almost all children are infected with RSV at least once by 2 years of age. The primary infection in an

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TABLE. **Characteristics of Common Cold Weather Viruses**

CHARACTERISTIC	RSV	INFLUENZA	HMPV	PIV	ADENOVIRUS	RHINOVIRUS
Seasonality	Begins early winter, peaks January or February, ends early spring	Begins late December and January (predominant strain A), ends early spring (predominant strain B)	Present throughout the year, peaks late winter and early spring	PIV-1 and -2 are seen in fall, PIV-3 in spring and early summer	Activity is present throughout the year, strains 3 and 7 cause respiratory disease	Year-round, with peak in winter months, September–May
Incubation period, d	2–8	2–3	5–9	2–4	5–7	2–3
Common clinical features	Fever Rhinorrhea Congestion Bronchiolitis Viral pneumonia	Fever Pharyngitis Cough Gastrointestinal symptoms Malaise Myalgias	Fever Rhinorrhea Congestion Bronchiolitis Viral pneumonia	PIV-1 and -2: croup PIV-3: bronchiolitis, viral pneumonia	Fever (prolonged) Pharyngitis Conjunctivitis Laryngotracheitis Pneumonia Pneumonia, hepatitis, cystitis, colitis in immunocompromised patients	Common cold with nasal discharge and cough Increased severity and duration of asthma
Preferred method of testing	PCR assay Sn 100% Sp 89% Other Rapid antigen Cell culture	PCR assay Sn 86%–100% Sp 89% Other Rapid antigen Sn 54%, Sp 100%	PCR assay Sn 94% Sp 99%	PCR assay Sn 95%–100% Sp 95%–100%	PCR assay Sn 83%–90% Sp 98% Other Serology Cell culture	PCR Sn 90%–100% Sp ∼95% Reported separate or with enterovirus Rhinovirus + PCR in infants likely represents infection within 30 d
Treatment	Supportive	Supportive or oseltamivir	Supportive	Supportive (dexamethasone for croup)	Supportive (cidofovir in immunocompromised patients)	Supportive
Prevention	Hand hygiene	Hand hygiene, annual vaccination	Hand hygiene	Hand hygiene	Hand hygiene	Hand hygiene
	Palivizumab in high-risk patients	Antiviral drug prophylaxis				Investigational: interferon-γ, pleconaril

hMPV=human metapneumovirus, PCR=polymerase chain reaction; PIV=parainfluenza virus, RSV=respiratory syncytial virus, Sn=sensitivity, Sp=specificity.
Data from the work of Joseph Greensher, MD (unpublished data).

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infant is almost always symptomatic, ranging from mild upper respiratory tract symptoms to severe bronchiolitis. A 2- to 4-day illness with low-grade fevers, rhinorrhea, and nasal congestion (upper respiratory tract symptoms) is followed by cough, tachypnea, and increased respiratory effort manifested by subcostal, intercostal, supraclavicular retractions; nasal flaring; and grunting (lower respiratory tract symptoms). (10) Bronchiolitis is more commonly the manifestation of primary RSV infection in infants as opposed to young children 2 to 5 years of age. Lower respiratory tract disease occurs more frequently in children with underlying cardiopulmonary disease, those in closed populations such as group child care centers, and children of American Indian and Alaskan native background. Viral pneumonia in RSV infection can coexist with bronchiolitis without evidence of secondary bacterial infection.

Course of Illness. The course of bronchiolitis varies and may require serial observations to adequately assess illness acuity. The decision to hospitalize an infant with RSV infection can be challenging. Among the more consistent and reliable findings in severe RSV disease are decreased oxygen saturations; therefore, hypoxia (oxygen saturation ≤90%) in an infant should be considered an indication for further inpatient monitoring. Rapid fluctuations in clinical manifestations are characteristic of RSV; therefore, serial assessments in either the office or the hospital are helpful.

Typical Findings on Examination and Chest Radiography. The auscultatory findings of bilateral crackles and scattered wheezing may be present on the initial examination and absent thereafter; this variability in physical examination findings within hours is characteristic of RSV infection. The chest radiography findings in RSV infection include hyperinflation with hyperlucency of the lungs, flattened diaphragm, and peribronchial thickening. Patchy areas of atelectasis may be present, more frequently in the right middle and upper lobes. Areas of atelectasis may be large and misinterpreted as consolidation. The current AAP guidelines do not recommend a routine chest radiograph because bronchiolitis is diagnosed based on clinical and physical clues and the radiography findings do not aid in management decisions. In fact, the finding of an infiltrate may increase the risk of inappropriate antibiotic drug use. Bacterial pneumonia in infants with bronchiolitis without consolidation is unusual. Antibiotic drug therapy may be justified in rare cases of bronchiolitis in which intubation and mechanical ventilation for respiratory failure are required.

Complications. Apnea may be present at the onset of illness in 1% to 20% of hospitalized infants. Most of the infants do not have apnea later in the course of infection or with subsequent infections. Apnea is more frequent in premature infants, at young chronological age (≤1–2 months), and in infants with a history of apnea of prematurity.

Coinfection with bacterial pathogens is rare in RSV infection and was found in 1.2% of children infected with RSV in 1 study. (11) Urinary tract infection is the most frequent secondary bacterial infection. Respiratory disease from bacterial coinfection with *Streptococcus pneumoniae* or *Staphylococcus aureus* is uncommon. Codetection of RSV with other viral pathogens is seen in approximately one-third of the cases using multiplex PCR assay; however, the significance of this finding on morbidity and length of stay is not clear. (12)

Diagnosis

A presumptive diagnosis of RSV infection is made based on either upper respiratory tract symptoms or bronchiolitis in infants and young children in the winter months. Routine testing of outpatients and hospitalized patients with bronchiolitis is not recommended in the clinical practice guidelines.

When to Test? Clinically it is not possible to distinguish between different viruses as the cause of bronchiolitis. Therefore, viral testing is useful for epidemiological monitoring, cohorting patients in the hospital, and providing a definitive diagnosis. In this era of antimicrobial stewardship, use of viral testing has shown mixed results in limiting antibiotic drug use. In our institution, stewardship efforts to reduce antibiotic drug use in confirmed RSV infection were possible with the availability of these objective data. (13)

What Tests to Use? During the past 5 to 10 years, the availability of multiplex PCR has proved to be the most sensitive method of viral detection. Other methods for RSV detection, although less commonly available, include standard culture or shell viral assay as well as immunoassays. Antigen detection assays for RSV are less sensitive than PCR but have good specificity and are less expensive.

There are 6 commercially available multiplex PCR assays (nested PCR), with sensitivity and specificity of 100% and 89%, respectively, with some variability in performance. (14) The average duration of RSV detected by PCR is approximately 11 days, but it can be up to 4 weeks in young infants and immunocompromised older children. Given the increased sensitivity of PCR, it can detect low-level asymptomatic shedding in the convalescent phase from a previous RSV infection, although prolonged asymptomatic shedding is not as common as seen with other viruses, such as RV. (15)

A dipstick immunoassay from a nasopharyngeal specimen allows the capture and visual detection of RSV fusion protein, which can be used as a rapid test in the office setting. It can provide results in 15 minutes and has pooled sensitivity and specificity of 81% and 97%, respectively, in children. (16)

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Serological testing is reserved for epidemiological research purposes because it is generally not helpful in the diagnosis of acute RSV infection. In the past, viral culture was the standard, but it takes 3 to 5 days to observe a syncytial cytopathic effect, in addition to the expertise required.

Treatment

The mainstay of treatment in infants and young children with RSV infection is supportive care, mainly attention to hydration and respiratory support. The use of bronchodilators, corticosteroids, or inhaled hypertonic saline is not recommended by the clinical practice guidelines because no benefit has been confirmed with these treatment modalities.

When to Use Ribavirin? Ribavirin is a nucleoside analogue that is Food and Drug Administration (FDA) approved for the treatment of RSV via small particle aerosol. However, it is not recommended because of unproven efficacy, expense, and potential untoward adverse effects from environmental exposure. Its use in RSV infection is limited to severely immunocompromised hosts with severe RSV infection, and even in these patients the question of benefit remains.

Prevention

Prophylaxis. Immunoprophylaxis against RSV is attainable with palivizumab. It is the only product available to reduce the risk of RSV infection. It is a humanized monoclonal antibody that targets a highly conserved epitope on the RSV F glycoprotein. Two randomized, multicenter, double-blind, placebo-controlled trials have shown a reduction in RSV-related hospitalization by 50% to 55%. (17)(18) It was approved by the FDA in 1998.

The current AAP guidelines recommend prophylaxis with palivizumab in:

1. Otherwise healthy infants who were born at less than 29 weeks 0 days of gestation plus 12 months or younger at the start of the RSV season. (19)
2. Infants in their first year after birth who have chronic lung disease using the definition of a requirement for supplemental oxygen through the first 28 days of life and again in their second year of life if they continue to require medical therapy (largely oxygen) for chronic lung disease within 6 months of the onset of the RSV season.
3. Infants younger than 12 months with acyanotic or cyanotic heart disease who are receiving medication to control heart failure and will require cardiac surgery.

Palivizumab is administered intramuscularly at a dose of 15 mg/kg once every 30 days throughout the RSV season up to 5 doses. Currently, studies of monoclonal preparations with longer half-life and increased affinity for the virus are underway and, if successful, could allow prophylaxis with a single dose.

Improved understanding of the structure of RSV and the importance of the prefusion protein has led to a tremendous increase in RSV vaccine development during the past decade. Approximately 60 vaccine candidates are in different stages of development. This vaccine pipeline is diverse and promising, and a safe and effective vaccine may well be available in the next 5 to 10 years.

Another important aspect of prevention of RSV infection in high-risk infants is education of caregivers on hand hygiene, avoidance of crowded places, and reduction of secondhand smoke exposure. Palivizumab does not have a role in treatment of RSV infection or in preventing nosocomial transmission of infection.

INFLUENZA VIRUS

Introduction

Influenza infection typically occurs during the late fall through early spring in the United States, peaking typically in February in most of the country. (20) Influenza is a significant cause of morbidity and mortality in children. (20)(21) Symptoms of uncomplicated infection typically include fever, chills, headache, malaise, myalgia, and nonproductive cough. Nasal congestion, sore throat, otitis media, and myositis may also occur. Nausea, vomiting, and diarrhea are more common in children than in adults. (22) However, young children (<5 years of age) commonly present only with signs of a febrile upper respiratory tract infection, whereas older children (≥ 5 years of age) may additionally report headache, malaise, and myalgia. In infants, influenza can cause various lower respiratory tract infections, including croup, bronchiolitis, and/or pneumonia. (23)

Prompt identification of high-risk persons with influenza infection is crucial because they are at increased risk for complications. High-risk persons include children younger than 5 years (and especially <2 years, who have higher rates of hospitalization for complications), those with chronic disease (including, but not limited to, asthma, sickle cell disease, diabetes mellitus, cerebral palsy, seizure disorders, and moderate to severe developmental delay), immune compromise, and morbid obesity (BMI ≥ 40). (20) Complications of influenza may include secondary bacterial infections (most commonly *S aureus*, group A *Streptococcus*, and *S pneumoniae*), myocarditis, encephalitis, respiratory failure, shock, and/or a sepsislike illness. (23)

Diagnosis

The Centers for Disease Control and Prevention (CDC) advocates clinically diagnosing influenza infection based on signs and symptoms in the appropriate epidemiological

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setting. (24) An influenzalike illness is defined as fever (temperature ≥100°F [≥37.8°C]), cough, and/or sore throat in the absence of another known cause. (23) Confirmation by diagnostic testing is not required, and neither should it delay initiation of antiviral medication. (25) However, clinical diagnosis of influenza in pediatrics is somewhat restricted because there are many shared signs and symptoms with other respiratory pathogens. Younger children (<6 years of age) have particularly greater overlap. (20) Furthermore, the epidemiology of coinfections with influenza remains difficult to assess secondary to lack of outpatient diagnostic information. (22)

These challenges can ideally be overcome with diagnostic testing, which can provide important clarifications about etiology. Specimens for diagnostic testing should ideally be collected within the first 72 hours of illness because the quantity of viral particles shed decreases as illness progresses. (23) Molecular assays, especially reverse transcriptase PCR tests, are highly accurate and considered the gold standard of testing. These assays can detect nucleic acids in respiratory specimens for extended periods and have improved sensitivity compared with rapid antigen detection assays. (26) Although less expensive and more available, clinicians must consider the heightened potential for false-negative results when using rapid antigen modalities during the peak of influenza season. The positive predictive value of rapid antigen tests will be lower during periods of low influenza activity. (27)

Treatment

Severity of disease, duration of symptoms, and presence of underlying conditions are important considerations when deciding to administer antiviral drug therapy. Antiviral drugs for influenza are most beneficial when started as close to illness onset as possible. The Infectious Diseases Society of America recommends prompt treatment (ideally, <48 hours from the start of symptoms) for patients in high-risk groups or those who are severely ill for 1 to 5 days. (24) Recently, Malosh et al (28) reported the findings from a meta-analysis of 5 randomized controlled trials of early oseltamivir treatment. Oseltamivir treatment started within 24 hours of onset reduced illness duration significantly more than when started 24 to 48 hours after onset (22.8 versus 4.4 hours). Oseltamivir, a neuraminidase inhibitor, acts as a competitive inhibitor by binding in the enzyme's active site. The primary function of the neuraminidase enzyme in the life cycle of influenza viruses is to remove sialic acid residues from the surface of the infected cell and from mucins in the respiratory tract, facilitating the release of newly synthesized virus particles and allowing the virus to spread. Early blockade of this activity by neuraminidase inhibitors prevents virion budding and leads to aggregation of viruses on the cell surface, preventing subsequent infection of new cells.

Any person requiring hospitalization for influenza should be treated empirically because they are at greater risk for complications. In hospitalized patients, treatment with oseltamivir up to 96 hours after illness onset has been shown to reduce severe clinical outcomes. In patients with prolonged illnesses, clinical judgment should guide the need to extend treatment beyond 5 days. (29) In the outpatient setting, patients who are not at high risk should be considered for treatment only if presenting within 48 hours of illness onset because it may also provide some benefit (eg, a shorter duration of illness). (24)(25)

There are 3 antiviral medications currently available to treat influenza in children: oral oseltamivir (treatment in infants 1–8 months old: 3 mg/kg per dose twice daily; 9–11 months old: 3.5 mg/kg per dose twice daily; children 12–23 months old: weight ≤15 kg: 30 mg twice daily for 5 days, weight >15–23 kg: 45 mg twice daily for 5 days; and children ≥2–12 years old and adolescents: weight ≤15 kg: 30 mg twice daily for 5 days, weight >15–23 kg: 45 mg twice daily for 5 days, weight >23–40 kg: 60 mg twice daily for 5 days, weight >40 kg: 75 mg twice daily for 5 days; prophylaxis is not recommended <3 months of age, >3 months the dose is same as treatment and the duration is 7 days), inhaled zanamivir (children ≥5 years old and adolescents: 2 inhalations [10 mg] once daily for 10 days), and, most recently, intravenous peramivir (children ≥2 years old: 12 mg/kg as a single dose; maximum dose: 600 mg per dose; adolescents: 600 mg as a single dose). All 3 of these medications inhibit viral neuraminidase activity and prevent viral release from host cells. To date, resistance has not been a clinically significant occurrence. (20)(22)(23) A new antiviral agent, baloxavir was approved in October 2018 for use in patients older than 12 years with uncomplicated influenza. It is a cap-dependent endonuclease inhibitor and requires single-dose administration. As per the AAP recommendations, oseltamivir is the drug of choice for the treatment of influenza in children and may be used in infants 14 days and older, although there is limited efficacy and safety data in children younger than 3 months. (29) The FDA approves treatment with oseltamivir for children as young as 2 weeks. (30) Peramivir is approved for acute influenza in children 2 years and older. Zanamivir, administered by disk inhaler, may be used as an alternative in children 7 years and older. Recommended treatment dosages vary by the weight of the child.

The most common adverse events experienced with oseltamivir and peramivir use include vomiting and nausea. Zanamivir is licensed only for use in persons without underlying respiratory or cardiac disease. Less common

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adverse events of zanamivir may include diarrhea, nausea, sinusitis, bronchitis, cough, headache, dizziness, and ear, nose, and throat infections. (30)

Prevention

The best preventive measure against influenza is seasonal, yearly vaccination for children 6 months and older. (22) There are 2 forms of the vaccine: an inactivated form administered intramuscularly and a live-attenuated form administered intranasally. (23) In previous influenza seasons, the Advisory Committee on Immunization Practices recommended exclusive use of the inactivated influenza vaccine after data showed decreased effectiveness (especially for H1N1 influenza strains) with use of the intranasal formulation. Currently, there is new evidence to support the use of a reformulated live-attenuated formulation, and the Advisory Committee on Immunization Practices has voted to recommend both vaccines for protection for the 2018-2019 season. (21) However, the AAP strongly recommends preferential use of the inactivated vaccine. (31) Influenza vaccine effectiveness is moderate, and a history of influenza vaccination in the season does not exclude an influenza diagnosis. Individuals with egg allergies may safely receive the vaccine without any additional precautions.

Chemoprophylaxis with antiviral medication is not a substitute for influenza vaccination. When deciding whether to administer chemoprophylaxis, the exposed person's risk of complications and the type and duration of contact should be considered. Oseltamivir is FDA approved for chemoprophylaxis of influenza in children 3 months and older. Zanamivir is approved for chemoprophylaxis of influenza in children 5 years and older. Peramivir is not currently approved for preventive use in children. (24)(25)

To achieve maximum efficacy, antiviral drugs for preexposure chemoprophylaxis must be taken for the duration of influenza exposure. However, extended use of these drugs may select for resistance, and the adverse effects associated with prolonged use are unclear. Oseltamivir use for up to 42 days has been well tolerated, but there are no published data available for longer regimens. (32) Preexposure chemoprophylaxis should be reserved for persons at very high risk for complications.

Postexposure chemoprophylaxis is indicated within 48 hours for close contacts of a person with influenza and is typically given for 10 days after the reported exposure. Candidates include unvaccinated household members or other close contacts at higher risk for complications. Note that persons receiving chemoprophylaxis may still acquire influenza infection and be potentially able to transmit influenza virus. (23)(24)(25)

PARAINFLUENZA VIRUS

Among the PIVs, the most common type is PIV-3, acquired by two-thirds of infants by 12 months of age. (33) PIV-1 infections occur most commonly in the fall as the weather turns colder. PIV-2 disease has more sporadic seasonal activity, and PIV-3 is most prominent during spring and summer but may continue into the colder months of fall. (33)(34) The seasonality and clinical manifestations of PIV-4 infection are less well described. (35) Most PIV infections affect the tracheobronchial and lower respiratory tracts, but influenzalike illnesses have also been reported. PIV-1 is the major cause of croup (laryngotracheobronchitis), and, less commonly, PIV-2 has been isolated. (34)(35) PIV-3 is associated with pneumonia and bronchiolitis. (35) Seasonal PIV epidemics cause up to 75% of croup. (36) Reinfection with PIV is common because immunity is transient, but reinfections are typically milder and limited to the upper respiratory tract. As with other viruses, reverse transcriptase PCR assays are the most sensitive diagnostic method for detection of PIV. Currently, there is no vaccine available against PIV. Treatment is supportive because most PIV infections are self-limited. There are no specific therapies available for PIV, although several are in development. (33)(35) For example, an experimental antiviral, DAS181, is a sialidase fusion protein that cleaves the sialic acid–containing receptors of PIV in respiratory cells. It has been reported to successfully treat PIV in patients with hematopoietic cell and lung transplant when considered for compassionate use. For mild croup, dexamethasone given as a single oral dose has been shown to improve symptoms.

ADENOVIRUS

Although Adv infections occur year-round, epidemic respiratory disease may occur in the winter and early spring. (37)(38) Respiratory Adv infection has a broad spectrum of presentation, ranging from symptoms of "the common cold" to pneumonia. Adv may also cause pharyngitis/tonsillitis, keratoconjunctivitis, croup, bronchiolitis, otitis media, hepatitis, gastroenteritis, meningitis, or encephalitis. (39) The latter 2 infections are more common in young infants and the immunocompromised, 2 populations at high risk for developing severe disease secondary to lack of humoral immunity. (38)(40) PCR assays are the preferred diagnostic method; however, intermittent and persistent shedding after Adv infections

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may pose a challenge in interpreting PCR results. (39) Furthermore, immunocompromised hosts may shed the virus for weeks or longer. (38) Studies have shown that detection of Adv DNA in peripheral blood is indicative of a high risk of disseminated disease. (41) Treatment is supportive. (39) There is a live, oral Adv vaccine, targeted for serotypes 4 and 7, approved by the FDA in 2011 for exclusive use in military personnel aged 17 to 50 years at higher risk for lower respiratory tract infection from these serotypes. (38) Several studies have shown limited treatment success using various antiviral drugs, including cidofovir and ribavirin. (37) Cidofovir use is generally reserved for immunocompromised patients with severe, life-threatening infections. In a study of neonatal Adv infections, ribavirin or cidofovir treatment did not improve outcomes. (42)

HUMAN METAPNEUMOVIRUS

hMPV is a paramyxovirus discovered in 2001 associated with respiratory tract disease in children. In temperate regions it is present throughout the year, with peaks in late winter and early spring. (43) The incubation period is 5 to 9 days. hMPV causes both upper and lower respiratory tract disease in children. Similar to RSV, the upper respiratory tract disease presents as rhinorrhea, cough, and fevers and the lower respiratory tract disease presents as bronchiolitis, croup, pneumonia, or asthma exacerbation. (44) In contrast to RSV, the rate of hMPV-related outpatient visits remains similar in older children compared with younger infants. Thus, hMPV causes clinically significant disease throughout early childhood similar to influenza. (43) In healthy children, viral shedding is usually 7 to 14 days, but in immunocompromised individuals it can be prolonged. (45) hMPV has been associated with neurologic manifestations, including febrile seizures, status epilepticus, and encephalopathy. (46) Molecular technology based on nucleic acid amplification assay can reliably diagnose hMPV infection. (47) The treatment is mainly supportive care. Ribavirin and oligoclonal immunoglobulins possess anti-hMPV in vitro activity, (48) but there is no proven benefit in management besides anecdotal reports in immunocompromised hosts. (49) There is no available vaccine or prophylactic antibody for prevention, but there are several candidates in development.

RHINOVIRUS

RVs are one of the most common causes of common cold and account for almost 50% of the upper respiratory tract infections in children and adults. (50)(51) RVs are members of the *Enterovirus* genus in the family *Picornaviridae.* Other members of the *Enterovirus* genus include polioviruses, Coxsackie viruses, and echoviruses. (52) RVs cause infections year-round, with seasonal peaks during the cold weather months, September through May. (53)

RV infections in any age group typically cause only mild upper respiratory tract illness. Children can have fever during the first 2 to 3 days and moderate enlargement of the anterior cervical lymph nodes. Illness generally lasts 5 to 7 days in adults, but it can persist for 10 to 14 days in children. RVs have been identified in several studies as the second most common viral infection identified in association with bronchiolitis after RSV. (54)(55) An infection with either RSV or RV that results in a wheezing illness during the first year of life is an independent risk factor for wheezing later in childhood. (56)(57) When RV is identified as the sole pathogen in a transplant recipient with lower respiratory tract infection, it can cause severe pneumonia with a clinical picture similar to that of influenza-associated pneumonia. (58)

The availability of multiplex PCR assays has revolutionized the diagnosis of RV. Because RVs have many nucleotide sequences in common among the RNA genomes of the various serotypes, especially in the noncoding region at the $5'$ end, the PCR assays have been designed and widely used for the detection of RVs, often in panels with other respiratory viruses. Some assays do not distinguish RVs from enteroviruses, whereas others are RV specific. (59)(60) Prolonged shedding can confound interpretation of a causal role in clinical settings (45) and is common in infants younger than 3 months.

There is no effective treatment available for "RV colds." Intranasal administration of interferon-α to the family members after symptoms appeared in the index case prevented 80% of the secondary RV cold cases. (61) The disadvantage of interferon-α prophylaxis is prolonged administration (>7 days needed) and repeated treatment produces an inflammatory response manifesting as nasal stuffiness, ulceration, and blood-tinged discharge. A capsid-binding agent, pleconaril, has in vitro antiviral activity against many enteroviruses and RVs, and phase 3 clinical trials on naturally acquired colds demonstrated some reduction in the severity and duration of several respiratory symptoms. (62)

Antihistamines, decongestants, and antitussives have not been shown to be effective in children with colds. (63) Development of a vaccine is hindered by the large number of serotypes and the serotype specificity of immunity.

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Summary

- Respiratory syncytial virus (RSV) and influenza account for most of the cold weather infections. Other important viruses responsible for respiratory infection in children include parainfluenza virus (peak in fall and spring), human metapneumovirus (peak in late winter and fall but activity is seen throughout the year), respiratory adenovirus (throughout the year), and rhinovirus (year-round with peak in cold weather).
- Based on strong clinical evidence, (5) RSV is the most common cause of bronchiolitis in infants and young children.
- Based on expert and consensus opinion, (2) clinicians should not routinely obtain radiologic or laboratory studies in cases of bronchiolitis. In addition, clinicians should not administer medications such as albuterol, epinephrine, and antibiotics in viral bronchiolitis.
- Based on analysis and interpretation of data, (19) palivizumab should be reserved for high-risk infants such as those born at or before 29 weeks of gestation, infants with chronic lung disease, and infants with congenital heart disease who continue to require treatment for their underlying condition until 24 months of age.
- Based on expert opinion, (24) influenza treatment should be considered in high-risk patients and in hospitalized children, ideally within 48 hours of symptom onset. The antiviral agent of choice is oral oseltamivir.
- Based on strong evidence, (35) parainfluenza 1 and 2 are a major cause of croup in the fall, and primary management is supportive care.
- Based on consensus, (41) the mainstay of treatment in adenoviral infections is supportive care. There is limited evidence (38) for use of cidofovir, even in immunocompromised hosts.
- Based on strong research evidence, (44) human metapneumovirus is a paramyxovirus causing bronchiolitis illness similar to RSV, and there is no antiviral drug therapy available.
- Based on strong evidence, (50) rhinovirus is the most common cause of the "common cold" in children and adults. Its detection in the multiplex polymerase chain reaction may represent infection or asymptomatic shedding.

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1. A 5-week-old boy born at 34 weeks' gestation is brought to the emergency department (ED) by his parents due to a concern of "strange breathing." He has a 1-day history of nasal congestion. His father and 6-year-old brother who live in the home have had a recent upper respiratory tract infection. The family visits a maternal grandmother once a week, and she has recently had a "stomach flu." The baby is noted to have two 15- to 20-second pauses in his breathing while in the ED and is admitted to the hospital. A multiplex PCR from a nasopharyngeal specimen is positive for respiratory syncytial virus (RSV). Which of the following transmission mechanisms is most likely responsible for the RSV infection in this patient?
   - A. Direct contact with his brother's nasal secretions.
   - B. Fecal-oral transmission from his grandmother.
   - C. Large airborne particles from his brother.
   - D. Large airborne particles from his father.
   - E. Small airborne particles from his father.

2. A previously healthy 4-month-old girl is brought to the ED due to a 3-day history of nasal congestion and increasing cough in the past day. She has felt warm at home and her breastfeeding has progressively decreased during the past day. Her rectal temperature is 100.8°F (38.2°C), respiratory rate is 68 breaths/min, and oxygen saturation on room air is 87%. Bilateral wheezes are heard. After suctioning and supplemental oxygen her oxygen saturation is 96% and her respiratory rate decreases to 48 breaths/min. She is to be admitted to the hospital, which currently has a very high census on the pediatric inpatient service requiring 2 patients to be in the same room (cohorting). Which of the following is the most appropriate next step in management while in the ED?
   - A. Chest radiography.
   - B. Inhaled hypertonic saline therapy.
   - C. Inhaled ribavirin therapy.
   - D. Intravenous methylprednisolone therapy.
   - E. Nasopharyngeal swab for multiplex polymerase chain reaction.

3. A 2-month-old girl born in September at 26 weeks' gestation is in the NICU. She is no longer intubated but is still on supplemental oxygen. She does not have a history of congenital heart disease. Which of the following is the most appropriate active or passive immunization that this patient must receive at this time?
   - A. Inactivated influenza vaccine.
   - B. Live attenuated influenza vaccine.
   - C. Oral adenovirus vaccine.
   - D. Palivizumab prophylaxis.
   - E. Ribavirin prophylaxis.

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4. A previously healthy 6-month-old boy presents to the ED with a 2-day history of fever, nasal congestion, worsening cough, decreased activity, and posttussive emesis. Mom states that he is not breastfeeding well and his urine output has decreased. He appears ill but not lethargic. His temperature is 102.4°F (39.1°C), he is tachypneic with subcostal retractions, and his oxygen saturation on room air is 88%. Breath sounds are equal on the right and left with no crackles or wheezes. He is started on supplemental oxygen and his oxygen saturation increases to 94% and his respiratory distress improves. A rapid antigen assay is positive for influenza A. He is admitted to the hospital and is started on intravenous hydration in addition to continuing supplemental oxygen. Which of the following is the most appropriate next step in management?

   A. Chest radiography.
   B. Inhaled albuterol therapy.
   C. Inhaled zanamivir therapy.
   D. Intravenous vancomycin and ceftriaxone therapy.
   E. Oral oseltamivir therapy.

5. A 9-month-old boy presents to the office in September for a health supervision visit. He was born at 38 weeks' gestation and was noted to have a small ventricular septal defect at 2 weeks of age. He has been followed by pediatric cardiology and has not required surgical repair and is taking no medications. At his last visit to the pediatric cardiologist, mom was told that her son would probably not need surgery because the ventricular septal defect would most likely close spontaneously. He is growing and developing well. His examination findings are normal except for a grade 2 systolic murmur on heart examination. The boy has no allergies, but his 7-year-old sister is allergic to eggs. Which of the following is the most appropriate next step in management?

   A. Chemoprophylaxis with oseltamivir from November to April.
   B. Chemoprophylaxis with zanamivir if he is exposed to influenza.
   C. Inactivated influenza vaccine.
   D. Live attentuated influenza vaccine.
   E. Palivizumab therapy.

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Confidentiality and Consent in the Care of the Adolescent Patient

Sofya Maslyanskaya, MD,* Elizabeth M. Alderman, MD*

**Division of Adolescent Medicine, Children's Hospital at Montefiore, and Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY*

Practice Gap

Confidentiality protections are critical in the provision of comprehensive primary care of adolescent patients. The protections differ based on state laws and are limited by electronic health record documentation and billing operations of individual physician practices. Physicians need to strive to increase their knowledge regarding confidentiality protections for their adolescent patients. Moreover, physicians should understand their role in preventing possible confidentiality breaches.

Objectives

After completing this article, readers should be able to:

1. Define confidentiality, its limitations, and reasons for developmentally appropriate confidentiality protections for adolescents.
2. Recognize confidentiality protections for adolescents provided by state and federal laws, including the Health Insurance Portability and Privacy Act privacy rule.
3. Explain minor consent laws.
4. Describe the limitations and advantages of the electronic health record in providing confidentiality protections.
5. Identify concerns and solutions related to billing for confidential services.

CASE

A 16-year-old girl who has been your patient since birth presents to an appointment alone and requests testing for sexually transmitted diseases (STDs). She also does not want her parents to find out about this visit. How would you proceed?

Confidentiality and Autonomy

The provision of confidentiality and the ability of adolescents to consent for certain health concerns are the cornerstone of optimal adolescent health-care. (1) According to this tenet, information about an adolescent's health-care is not disclosed without his or her permission. Assurance of confidentiality is important to protect the adolescent's health and to safeguard public health. The major causes

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ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
EHR	electronic health record
EOB	explanation of benefits
HIPAA	Health Insurance Portability and Privacy Act
HIV	human immunodeficiency virus
SAHM	Society for Adolescent Health and Medicine
STD	sexually transmitted disease

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of morbidity and mortality in adolescents are due to risky behaviors such as sexual activity and alcohol and substance use, as well as unmet mental health needs.

During the past 3 decades, research has supported the importance of the provision of confidential health-care and illustrated that if not provided, adolescents and young adults will not seek out prescription contraceptives, receive screening and treatment for STDs, or disclose substance use to the providers at their medical home. (2)(3)(4)(5)(6) Moreover, they will withhold information from their health-care provider and may not return for subsequent visits. (7) During the adolescent years, adolescents transition from children to adults, and clinicians need to support the adolescent's individualization and developing autonomy. By ensuring confidentiality for certain health-care concerns, pediatricians are supporting this crucial milestone of adolescent development by fostering decision-making skills. This approach also reflects the physician's ethical obligation to ensure the patient's well-being and protect the nonautonomous. Because we wish to minimize harm, the ethical concept of beneficence is also in play when providing confidential care. Beneficence refers to the clinician's responsibility to prioritize the patient's well-being when making decisions about medical care. Therefore, the services that may be provided confidentially to adolescents are related to reproductive health, outpatient substance abuse, and mental health services.

For more than a quarter of a century, national medical organizations, including the American Academy of Pediatrics, the Society for Adolescent Health and Medicine (SAHM), the American Academy of Family Practice, and the American College of Obstetricians and Gynecologists have supported the need to provide confidential care for adolescents (Table 1). (8)(9)(10)(11) Not only do they call for such care, but they also advocate for education of adolescents and their parents about the importance of confidentiality, particularly for evaluation, testing, and treatment of STDs (including human immunodeficiency virus [HIV]), preventive reproductive health-care, contraception, and pregnancy-related services such as abortion.

It is essential to educate families, both parents/guardians and adolescents, on the reasons for clinicians requesting to spend part of the visit with the adolescent alone and starting to do this annually in early adolescence as part of best practices. Adolescents are frequently unaware of where they could obtain confidential services, especially substance abuse and mental health services, and do not use or envision their primary care providers as a resource. (12) The 11-year-old visit, when multiple vaccines are recommended and many children are on the brink of entering middle school, is a good time to start to engage in this conversation with parents and their preteens. Physicians should have discussions with the parent or guardian and the preteen or adolescent on the importance of adolescents having time alone with their physicians so that adolescents can voice their concerns to physicians and be encouraged to take responsibility for their health-care decisions. Physicians should continue to encourage open communication and discussions surrounding sensitive topics between parents and adolescents.

Primary care offices could create office policies describing adolescents' rights and share them with all new patients and families of preteens so as to normalize this essential aspect of adolescent health-care. This office culture should allow for improved trust and the potential for disclosures by adolescents and their parents. The SAHM recommends the

TABLE 1. **Position Statements and Opinions on Adolescent Confidentiality**

CONFIDENTIALITY	CONFIDENTIALITY AND THE EHR
American Academy of Pediatrics. Confidentiality in adolescent health care. *AAP News*. 1989	American Academy of Pediatrics. Standards for health information technology to ensure adolescent privacy. 2012
Confidential Health Care for Adolescents: position paper for the Society for Adolescent Medicine. 2004	Society of Adolescent Health and Medicine. Recommendations for electronic health record use for delivery of adolescent health care. 2014
American College of Obstetricians and Gynecologists. Confidentiality in adolescent health care. In: *Tool Kit for Teen Care*. 2nd ed. Washington, DC: American College of Obstetricians and Gynecologists; 2009	Committee on Adolescent Health Care. ACOG Committee Opinion no. 599: adolescent confidentiality and electronic health records. 2014
American Academy of Family Physicians. Adolescent health care, confidentiality. 2008	

EHR=electronic health record.

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training of front desk and billing staff so that they could provide appropriate guidance to patients on the confidential services available in their office. (9)

The ability of an adolescent to interpret health-care information provided to them and to adhere to recommendations is related to their cognitive development. The maturation of the adolescent brain generally occurs as the teen progresses from early to late adolescence. (13) Similar to physical pubertal changes, cognitive changes of adolescents are not age dependent and, therefore, age is not the determining factor in the adolescent's ability to make health-care decisions. Cognitive development advances as the adolescent progresses through early, middle, and late adolescence (Table 2). After age 18 years, adolescents have full legal rights as they become legal adults and are considered to have full adult reasoning. Parents may have or may apply for legal guardianship of their adult children with intellectual disabilities and, therefore, would have the power of attorney to make medical decisions for their adult child. It is less common, but possible, that parents are able to obtain legal guardianship of their adult children with mental health problems.

Intellectual abilities should also be considered when making the determination of capacity to consent. Depending on the level of intellectual disability, many adolescents cannot consent to treatment based on their capacity to understand the risks, benefits, and alternatives of the confidential services. These adolescents have to be evaluated by a physician to assess for their capacity to understand pros, cons, and alternatives for the treatments offered. Frequently, parents continue to be involved in reproductive decisions for adolescents with intellectual disabilities.

The degree of autonomy that the adolescent possesses is also crucial in determining the adolescent's competence to consent. By giving the adolescent the ability to make his or her own health-care decisions, the provider is supporting the adolescent's growth as a health consumer.

Relevant Legal Status Laws

Under the law, an adolescent younger than 18 years is generally considered a minor. However, minors younger than 18 years may have acquired legal status under one of the following provisions: mature minor, emancipated minor, incarcerated minor, or a minor in foster care. If a minor's status has been designated as any of these, they may be afforded some of the same legal rights as adults, and this affects their right to obtain confidential health-care.

Mature Minor. A mature minor is generally a minor who has sufficient intellect and autonomy to provide informed consent for medical care. When determining whether an adolescent is a mature minor, one must consider chronological age and developmental maturity, degree of autonomy, ability to adhere to medical care, and the seriousness of the illness versus risks of therapy. Clinicians need to evaluate whether a minor has the capacity to make voluntary decisions and weigh alternatives. For example, if the adolescent has been able to manage previous illnesses and adhere to medications/treatment, then the minor can be deemed competent to consent to their care if state law allows. However, minors generally cannot receive care for routine, nonemergent general health-care without parental consent.

Emancipated Minor. Emancipation, under the law, is defined as a surrender of parental rights to a child. Each state has laws defining circumstances where a minor may be considered emancipated. (14) Such circumstances may include a minor who is married, lives away from parents or legal guardians, is financially independent, is in the military, or whose parent/guardian has renounced their parental rights.

Pregnant and Parenting Teens. Pregnant teens can consent to their own health-care in most states, as well as that of their child. Questions do come up around the rights of teen fathers. Generally, if a teen is listed as the father of a child on the birth certificate, he would have the same parental rights

TABLE 2. Adolescent Development

DEVELOPMENTAL STAGE	AGE, Y	PSYCHOSOCIAL CHANGES
Early	~12–14	Concerned about physical appearance, concrete thinking Have difficulty considering long-term consequences of actions
Middle	~15–17	Peers and peer friendships are essential, experimentation stage
Late	~18–21	Decisions and beliefs are less influenced by peers Work toward mutual understanding in relationship with parents

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as the teen mother. However, it is quite variable as to whether a parenting teen can consent for their own health-care, unless it falls into the categories listed previously herein. Providers should reference the laws in their states.

Teens in Foster Care. Many states continue to allow parents or legal guardians to consent for medical treatment of their children after the children have entered into foster care. To streamline the consent procedure, many foster agencies have the parents sign a consent form for routine services, which is available from the child's welfare worker. (15) For teens whose parents are not available or not cooperative, courts make decisions to appoint a guardian or have the welfare commissioner provide consent for services outside of routine care, such as psychotropic medication prescription or surgical procedures. If a teen in foster care requires emergency medical attention and a legal guardian is not available, a physician could provide services without parental consent if their state law allows this. Teens in foster care could consent to confidential services based on their state laws similar to other teens residing in their states and if they have the capacity to consent.

Relevant Federal and State Laws

Another important consideration when determining the possibility of ensuring confidential health-care for minor adolescents are federal and state laws that govern the minor's ability to consent for medical treatment. Federal laws override state laws and, therefore, basic knowledge of both is necessary to decide on the services that could be offered to the adolescent without parental consent (Fig).

Federal Laws. There are few federal laws related to the provision of confidential health-care. A federal privacy rule was established in 2002, based on the 1996 Health Insurance Portability and Privacy Act (HIPAA) to allow the minor children to access their health information if it is related to confidential services or if they receive court approval to obtain those services and, therefore, have authority over their medical records. Parents cannot access these records unless permitted by their minor child (Table 3). (3)

Furthermore, the federal privacy rule ensures confidentiality for all health information to patients 18 years or older. (16) It is important to remember that for these patients, *all* health information must be kept private from parents, unless the adult child consents to disclosure of their health information. Health-care providers sometimes overlook this point because they have cared for the patient throughout childhood and are accustomed to the parent overseeing the child's health-care. The parents of adult children need to be educated about HIPAA, as do the adult children.

Title X of the Public Health Service Act is federal legislation that provides grants to organizations to assist with family planning and related preventive health services and requires programs that it funds to provide confidential services for adolescents. (17)(18) Similar rules exist for federally supported substance and alcohol use programs which receive grant funding and review by the Substance Abuse and Mental Health Services Administration. (19) Recipients of Medicaid insurance also have specific federal laws that require confidential protections for adolescents and are used to prevent confidentiality breaches. The HIPAA privacy rules defer to federal law surrounding these programs.

State Laws. Laws around adolescent confidentiality are generally state specific and may be complex. A variety of states give physicians permission to disclose information to parents or guardians that could be considered confidential, such as treatment for STDs. State laws often reflect legislation but also could be based on case law of the courts and statutes. These laws often weigh the tenets of family law (the status of minor children and the responsibilities and rights of parents/guardians) against the rights of the individual.

Most states have laws ensuring confidential care for minors based on the type of medical services requested, specifically, sexual health (STDs, contraception, pregnancy, and pregnancy options), outpatient mental health, outpatient

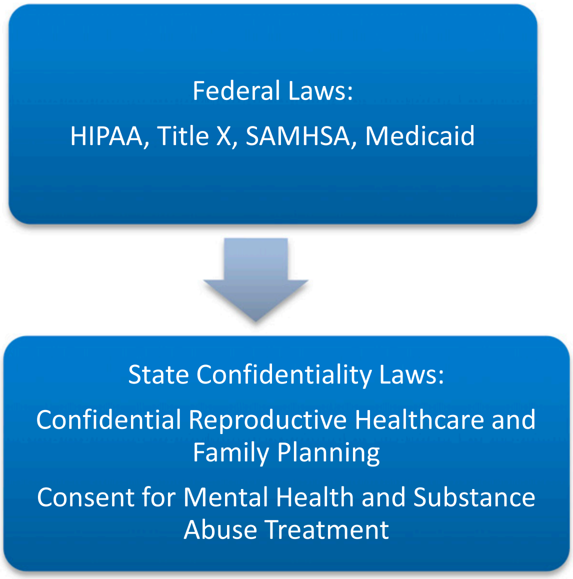
Federal Laws:
HIPAA, Title X, SAMHSA, Medicaid
State Confidentiality Laws:
Confidential Reproductive Healthcare and Family Planning
Consent for Mental Health and Substance Abuse Treatment

Figure. Laws governing adolescent confidentiality in the United States. HIPAA=Health Insurance Portability and Privacy Act, SAMHSA=Substance Abuse and Mental Health Services Administration.

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TABLE 3. Resources with Information on Federal and State Laws on Confidentiality

RESOURCE	WEBSITE
Centers for Disease Control and Prevention. HIPAA privacy rule and public health: guidance from CDC and the U.S. Department of Health and Human Services.	https://www.cdc.gov/mmwr/preview/mmwrhtml/m2e411a1.htm
Office of Population Affairs. Program requirements for Title X funded family planning projects.	https://www.hhs.gov/opa/sites/default/files/ogc-cleared-final-april.pdf
Electronic Code of Federal Regulations.	https://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&sid=b7e8d29be4a2b815c404988e29c06a3e&rgn=div5&view=text&node=42:1.0.1.1.2&idno=42%20-%20se42.1.2_114
Policy Compendium on Confidential Health Services for Adolescents. 2nd ed.	http://www.cahl.org/PDFs/PolicyCompendium/PolicyCompendium.pdf
State Minor Consent Laws: A Summary. 3rd ed.	https://www.freelists.org/archives/hilac/02-2014/pdftRo8tw89mb.pdf
Guttmacher Institute. State policies in brief: an overview of minors' consent law. 2018	https://www.guttmacher.org/state-policy/explore/overview-minors-consent-law
What can parents do? A review of state laws regarding decision making for adolescent drug abuse and mental health treatment. *J Child Adolesc Subst Abuse.* 2015;24(3):166–176.	

alcohol and substance abuse, and diagnosis and treatment for sexual assault. (20) These laws are based on the need for privacy inherent to these categories of health-care, as well as the normative adolescent development of autonomy, as described previously herein. All states, generally, allow for the provision of confidential services for minor adolescents for the prevention, screening, diagnosis, and treatment of STDs and sexual assault. There may be exceptions related to the screening, prevention, and treatment of HIV infection and AIDS, as well as vaccinations (human papillomavirus, hepatitis B, hepatitis A). Most states require parental consent for treatment of HIV/AIDS, as well as immunizations. The minor's permissibility to access confidential care for contraception, prenatal care, care for their own child, mental health, and outpatient alcohol and substance abuse varies among states but in many cases is permissible, albeit with some restrictions. Only 2 states and the District of Columbia allow minors to consent for termination of pregnancy. If a state does not allow a minor to consent to termination of a pregnancy, a system of judicial bypass must exist so that a minor may petition the court for the ability to consent for termination of pregnancy. This may be a difficult process for an adolescent and requires access to a legal advocate and psychosocial support. The Alan Guttmacher Institute maintains a current listing, by state, of what reproductive health-care services may be provided confidentially. (20) State laws provide the ability for adolescents or their parents to provide consent for inpatient and outpatient substance use disorder and mental health treatment and vary widely. A study by Kerwin et al (21) in 2015 found that one-third of the states have inconsistent laws on the consent requirements for mental health vs substance abuse treatment, including 15% of the states allowing only the minor to consent for drug use treatment.

Privacy of Health Information

Exceptions to Confidentiality. There are circumstances when a minor's confidentiality cannot be maintained and the health-care provider is mandated to disclose private information. Providers must be aware of their state's legal requirements, such as reporting child abuse. Clinical and professional judgment is essential when assessing patients for abuse and exploitation. Moreover, if an adolescent is deemed to be harmful to self or others, confidentiality must be broken. It is essential that these limits of the provision of confidential health-care be discussed with adolescents and parents/guardians as part of the general discussion on adolescent confidentiality.

Another exception to the assurance of confidentiality is the diagnosis of STDs such as gonorrhea, chlamydia, syphilis, and HIV that are in the category of reportable diseases.

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It is required that positive results are reported to local departments of health and, ultimately, the Centers for Disease Control and Prevention (CDC). This is in the interest of public health and allows the health department to assist in the notification and treatment of sexual partners so that these infections become less transmissible to the general population.

Additionally, there is no authorization required for the automatic release of information to health insurance plans or health-care providers who are involved in the care of the patient. (3)(22)

Electronic Health Record. Adolescents and young adults have the highest rate of Internet use and, therefore, are most likely to benefit from medical information becoming available electronically. (23) They are also the group that needs the most protection in this electronic generation. In 2009, the Health Information Technology for Economic and Clinical Health Act was issued by the US Department of Health and Human Services to increase HIPAA protections and improve the delivery of health-care through health information technology use. (24) This has led to a more widespread use of electronic health records (EHRs), which are systems that allow the sharing of information within a health-care organization and include clinical visit notes, test results, and problem and/or medication lists. In 2012, almost 4 of every 5 pediatricians were using an EHR. (25) The American Academy of Pediatrics, SAHM, and American College of Obstetricians and Gynecologists have published policy statements emphasizing the importance of adolescent confidentiality protections in EHRs and advised that the protections should be guided by the established federal and state laws (Table 3). (26)(27)(28)

An additional challenge to the provision of adolescent confidential services has been the rollout of the meaningful use requirements by the Centers for Medicare and Medicaid Services in the Department of Health and Human Services in 2010. Meaningful use requirements are used to monitor health providers' improvements in EHR utilization and are used for reimbursement purposes. (29) One of the requirements is the provision of a clinical summary printout after each medical visit. In the case of an adolescent who comes in with a parent and is seen for part of the visit alone, some of the laboratory tests, medications ordered, and problems added to the problem list could pose a risk to confidentiality protections. Strategies that could be used to prevent breaches in confidentiality include the restriction of the confidential diagnoses, medications, and laboratory tests from the clinical summary printout for adolescents younger than 18 years and distribution of the summary directly to patients older than 18 years.

Another meaningful use requirement is to allow patients or their representatives access to a secure Internet portal that contains their health information, including diagnostic test results, problem lists, and medications and/or opportunity to communicate with their physicians through a secure e-mail. This provides a challenge to protection of confidentiality, while also being an important tool that could be set up to allow for direct and improved communication between adolescents and their providers.

In their position paper, the SAHM recommends that medical providers be aware of their current EHR settings and actively advocate and improve protections for adolescents in their health-care system. (28) The SAHM also suggests the development of separate portals for adolescents and their parents, with limited exceptions for adolescents with serious medical illnesses and those with intellectual disabilities. An additional recommendation is the distinction between health information exchanges, which are designed to allow for medical information sharing between medical facilities, and the EHR, located in a single medical system. At the time of health information exchange creation, settings should be incorporated to prevent the release of sensitive information to other medical centers unless directly approved by the adolescent so that this information is not inadvertently shared with parents. (28)

Additionally, the automated reminder service that has been introduced by many pharmacies for patient convenience could pose a risk to confidentiality for adolescents and should be discussed at the time of medication prescription. (30) Possible solutions include providers offering teens the option of speaking with their parents about the medication being prescribed, checking with the pharmacy regarding their use of automated reminders, or sending the prescription to a different pharmacy than the one used by the family.

Billing. If an adolescent chooses to obtain confidential services, he or she needs to be aware of the possible breaches to confidentiality at the time of billing and payment by their health insurer. Explanation of benefits (EOB) is a letter that is mailed to the primary insurance policyholder, generally the parents, at the time of the payment for the claim and includes information about the person who received the medical services and the services obtained during that visit. The intention of the EOB letter is to prevent billing fraud and provide patients with detailed information about what was paid by the insurance policy and what is the financial responsibility of the policyholder. (31) For adolescents, EOB

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letters could disclose sensitive information to their parents. Some states have started to address this issue in their insurance law in an attempt to prevent EOBs from being mailed out for certain, confidential services, with the modification of the law to include the opportunity for confidential communication. Confidential communication refers to the ability of owners of health information to ask for the EOB to not be mailed or to be sent by an alternative means, such as e-mail. California was the first state to enact this law, which went into effect in 2015. Similar laws/regulations are pending or have been approved into law in Oregon, Massachusetts, Maryland, and Washington. New York has enacted a law that has removed the requirement for the EOB to be sent if only a copayment was required that was paid at the time of the visit and the claim is fully paid, unless requested by the policyholder. (32)

The laws preventing release of EOBs are relatively new and not all-encompassing, so adolescents need to be educated about this possibility of breach of their confidentiality in the case of an EOB being mailed to their home, and adolescents should be counseled about alternative ways of obtaining confidential services. Many college health services and school-based clinics provide low cost or free care for reproductive, mental health, and substance abuse services. In addition, Title X–funded health programs, including Planned Parenthood, are centers where adolescents may obtain confidential screening for STDs and contraceptive management without billing concerns. Another alternative is a subsidized health insurance plan for family planning services that is available in 20 states in the United States as an expansion of Medicaid services. (33) Other options include the provision of reduced cost visits, or adolescents could be offered to pay for the services out of pocket to avoid the EOB letter.

Summary

For the 16-year-old girl who is requesting sexually transmitted disease (STD) testing:

- Based on evidence quality D, all states allow for confidential STD testing, but there are some states that may require the physician to disclose to parents any positive results, and you will need to reflect on the laws guiding practices in your state.
- Based on evidence quality D, she should be notified about the possibility of an explanation of benefits letter being sent to her home because of office billing and laboratory testing, thus possibly disclosing some sensitive information, and she should be notified of the alternative ways available for her to pay for these services, including information on how to obtain a subsidized health insurance plan if available in your state to maintain confidentiality.
- Based on evidence quality D, if your state does not offer subsidized health insurance plans you may need to refer her to Planned Parenthood or a public health clinic. Alternatively, you can counsel her on having her partner share some of the cost of her laboratory testing and subsidize the fee for her office visit.
- Based on evidence quality D, ensure that your office electronic health record has protections for adolescents and that no sensitive diagnoses, tests, or medications are printed on the after-visit summaries that could be easily seen by her parents. Moreover, ensure that you have designed your patient portal to disable release of laboratory results of adolescents younger than 18 years.
- Based on evidence quality D, with all these safeguards, you are able to assure your minor adolescent patient that her sensitive information will not be released to her parents without her permission. You encourage her to discuss her health with her parents. However, if she cannot, you can still provide confidential care for her reproductive and mental health.

References for this article are at http://pedsinreview.aappublications.org/content/40/10/508.

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1. A 16-year-old girl presents to the emergency department (ED) after sustaining a left ankle injury while playing basketball. Physical examination reveals a swollen left ankle. She is unable to bear weight. The initial impression is that this is likely a sprain, but a fracture cannot be ruled out. A urine pregnancy test is ordered before obtaining a radiograph. The ED physician receives a telephone call from the laboratory that her urine pregnancy test result is positive, and radiography is deferred. Which of the following is the ED physician's next best step in the management of this patient?
   A. Call her mother and notify her that her daughter is pregnant.
   B. Call her mother and ask her to have the patient call the physician back.
   C. Call her mother and ask her to follow up with the ED physician the next day and give her the pregnancy test results of her daughter in person.
   D. Break the news only to the patient, and encourage her to discuss the results with her mother.
   E. Send the patient to her pediatrician without giving her the results.

2. A 14-year-old girl is brought to the clinic by her mother after getting a call from school that she is skipping classes to be with her 21-year-old boyfriend. The mother is worried that her daughter is having sex. When interviewed alone, the patient seems withdrawn but denies everything. In addition to testing her for pregnancy, which of the following is the most appropriate next step in the management of this patient?
   A. Tell the patient with the mother in the room that a sexual relationship between a 21-year-old and a 14-year-old is illegal in your state and refer her for counseling.
   B. Send her to the ED to get a sexual assault examination because she is younger than 16 years and you are concerned about statutory rape.
   C. Refer her to the child abuse center for further evaluation.
   D. No follow-up is needed because the child denies everything.
   E. Call the clinic social worker and discuss the best option for the patient according to state laws.

3. A 17-year-old young man comes to the school clinic for a follow-up from a previous clinic visit to discuss positive results on sexually transmitted disease testing. He is positive for gonorrhea. He is in a boarding school where he lives alone in the dormitory. His parents live overseas where his father works. He has had a steady 16-year-old girlfriend for the past 6 months. You note that he is on his father's insurance plan. Which of the following is the most appropriate next step in management?
   A. Notify his parents of his laboratory results and withhold treatment until the parents give consent because he is a minor (<18 years of age).
   B. Report his results to the health department while waiting for his parental consent to treat.
   C. Treat him because he is considered an emancipated minor; reporting to the health department is not required.
   D. Treat him because he is considered an emancipated minor, treat his partner, report it to the health department, and counsel him that despite confidential billing his father can find out from the insurance bill.
   E. Treat him because he is considered emancipated minor, report it to the health department, and counsel him that because of confidential billing his parents will never know.

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4. A 2-month-old boy is brought to the clinic by his 16-year-old mother for his 2-month health supervision visit. The mother is accompanied today by the boy's maternal grandmother. Both parents are 16 years old, and they live with the maternal grandparents. The 2-month-old boy is due today for his first set of vaccines. Which of the following is the most appropriate plan regarding the consent for the required vaccines in this patient?

   A. Consent is required and needs to be given by the father.
   B. Consent is required and needs to be given by both grandparents because the parents are living with them.
   C. Consent is required and the 16-year-old mother can give consent for her child's vaccines.
   D. Consent is required and should be given by the maternal grandmother because the mother is only 16 years old.
   E. No consent is required because this is a routine office procedure and is covered under consent to treat.

5. A 14-year-old boy is brought to the ED with severe headaches and sleeping a lot. Mom reports that he has not been wanting to get out of bed and has missed a week of school. The patient is interviewed alone. Initial assessment in the ED shows a young man with depressive mood; he reports constant crying while alone, inability to sleep, and wishes to die. He reports that he has been depressed for months and recently his depressive symptoms have worsened after his uncle, whom he was close to, died a few weeks ago. He feels that life is not worth living anymore and is contemplating ways to kill himself. He asks not to tell his parents because they have been through a lot of family stressors lately. Which of the following in the next best step in the management of this patient?

   A. Arrange for a psychiatry outpatient appointment in 5 to 7 days.
   B. Respect the patient's confidentiality if he signs a contract promising not to kill himself.
   C. Have the patient follow up with his primary care physician.
   D. Inform him that you have to tell his parents, activate an emergency detention order, and admit the patient to an inpatient psychiatric center for evaluation and clearance.
   E. Prescribe him tricyclic antidepressants and have him follow up with his pediatrician.

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Pediatrics in Review 2019;40;508
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Necrotizing Enterocolitis: Enhancing Awareness for the General Practitioner

Fiona Wertheimer, DO,[*†] Roxanne Arcinue, MD,[†‡] Victoria Niklas, MD, MA[§]

*Division of Neonatology, Department of Pediatrics, LAC+USC Medical Center, Los Angeles, CA
[†]Keck School of Medicine, University of Southern California, Los Angeles, CA
[‡]Fetal and Neonatal Institute, Division of Neonatology, Department of Pediatrics, Children's Hospital Los Angeles, Los Angeles, CA
[§]Prolacta Bioscience Inc, Duarte, CA, and Department of Pediatrics, David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA

Practice Gaps

Necrotizing enterocolitis (NEC) affects mostly premature infants but may develop in term infants with congenital malformations, including heart disease, abdominal wall defects, and sepsis. Following standardized feeding guidelines and prioritizing human milk feeding have decreased the rate of NEC in preterm infants, and, therefore, these approaches should be a priority in all infants at risk for NEC.

Objectives

After completing this article, readers should be able to:

1. Describe the epidemiological risk factors for necrotizing enterocolitis (NEC) in preterm and term infants.
2. Understand the pathophysiology of NEC relative to infant risk factors.
3. Describe the clinical signs and symptoms and briefly outline management strategies for infants with suspected and confirmed NEC.
4. Discuss preventive measures, such as human milk feeding, and the mechanisms underlying these benefits.
5. Recognize long-term complications of NEC, including neurodevelopmental disability and intestinal failure, and the appropriate follow-up care.

Abstract

Necrotizing enterocolitis (NEC) has been recognized for well over 5 decades yet remains the most common life-threatening surgical emergency in the newborn. The incidence of NEC has decreased steadily in preterm and very-low-birthweight infants over several decades and is typically uncommon in term newborns and infants with a birthweight greater than 2,500 g. Evidence accumulating during the past decade, however, suggests that practitioners should consider NEC in this broader

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ABBREVIATIONS

NEC	necrotizing enterocolitis
PRBC	packed red blood cell
SIP	spontaneous intestinal perforation
TNEC	transfusion-associated NEC
VLBW	very low birthweight

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subset of term infants with chromosomal and congenital anomalies complicated by heart or gastrointestinal defects when signs and symptoms of feeding intolerance, abdominal illness, or sepsis are present. The short- and long-term consequences of NEC are devastating in all infants, and although early disease recognition and treatment are essential, promoting human milk feeding as a primary modality in prevention is critical. This article highlights our current understanding of the pathophysiology, the clinical presentation, the risk factors for NEC in term infants compared with premature infants, and the treatment of NEC and discusses strategies in the prevention of NEC. Finally, we review the long-term consequences of NEC and the importance of primary care practitioners in the long-term care of infants after hospitalization for NEC.

EPIDEMIOLOGICAL RISK FACTORS IN PRETERM AND TERM INFANTS

Necrotizing enterocolitis (NEC) has been recognized for more than 5 decades yet remains the most common life-threatening surgical emergency in the newborn, with dire short- and long-term consequences. (1)(2) Most NEC occurs in infants younger than 32 weeks of gestation and in very-low-birthweight (VLBW) infants (birthweight <1,500 g), although late preterm and term infants also develop NEC. (3)(4) The incidence of NEC is highest in infants born at less than 32 weeks of gestation, occurring in 1 to 3 per 1,000 live births. Although the national incidence of NEC varies, NEC affects 5% to 9% of VLBW infants. (5)(6)(7) In contrast, the incidence of NEC in term infants is significantly lower, with approximately 10% of all cases of NEC occurring in term infants. (8)

Unique risk factors for NEC have been described in preterm and term infants, although many risk factors are overlapping (Table 1). Prematurity is the most critical risk factor for the development of NEC, particularly in VLBW and small-for–gestational age infants (Table 1). (3) In more recent years, a history of packed red blood cell (PRBC) transfusion (9) has been associated with cases of NEC in VLBW infants; however, whether the degree of anemia or the response to transfusion is primary in the development of disease remains to be determined. (9)(10) Formula feeding, regardless of gestational age, is a common risk factor for all infants who develop NEC, whereas human milk feeding is protective. (6)(11)(12)(13) A history of birth asphyxia or hypoxia is present across gestational ages, although NEC may develop weeks after the event. (4) In late preterm and term infants, the development of NEC has also been linked to congenital malformations, including gastroschisis, chromosomal abnormalities, and congenital heart disease. In fact, congenital heart disease is 1 of the most common risk factors for NEC, with hypoplastic left heart syndrome and truncus arteriosus being the most common types associated with NEC. (4)(8)(14)(15) In addition, up to 20% of term infants with hypoplastic left heart syndrome develop NEC after Norwood palliation, suggesting that decreased perfusion to the gut, as well as hypoxemia, underlie the development of NEC. (16) However, as in preterm infants, late preterm and term infants may also develop NEC without predisposing risk factors. For this reason, practitioners must maintain a high index of suspicion for all infants with systemic signs of sepsis or feeding intolerance (Table 1). (8)(15) (17)(18)(19)

The onset of NEC is inversely related to gestational age such that the earlier the gestational age, the later the chronological age at which NEC develops. For example, the average age at onset is 20.2 days for infants born at less than 30 weeks of gestation, 13.8 days for infants born at 31 to 33 weeks of gestation, and 5.4 days for infants born after 36 weeks of gestation. In all infants, the timing of NEC onset often correlates with the timing of initiation or advancement of enteral feeds, which, in general, occurs earlier in term infants than in preterm infants. (8) The onset of NEC in term infants also highlights the impact of interventions such as surgery or exchange transfusion that increase an infant's risk of NEC. For example, the timing and recovery from surgical repair in gastroschisis or congenital heart disease or the completion of exchange transfusion may more accurately predict the period of risk for NEC than an infant's postnatal age. (14)(20)

The case fatality rate also varies with gestational age, with the smallest and least mature infants demonstrating the

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TABLE 1. **Risk Factors for Necrotizing Enterocolitis by Infant Category**

PREMATURE INFANTS (<32 WEEKS)	ALL GESTATIONAL AGES	LATE PRETERM AND TERM INFANTS
Very low birthweight (<1,500 g)	Formula feeding	Congenital heart disease
Small for gestational age	Hypoxia	Chromosomal abnormalities
Anemia in need of packed red blood cell transfusion	Hypotension requiring inotropic support	Gastroschisis
Patent ductus arteriosus	Birth asphyxia	Sepsis
	Intrauterine growth restriction	Postnatal respiratory distress
	Polycythemia	Hypoxic ischemic encephalopathy
	Chorioamnionitis	Milk protein allergy
	Exchange transfusion	Hypothyroidism
	Umbilical lines	Protracted diarrhea
	Premature rupture of membranes	Maternal history of preeclampsia
	Maternal cocaine use	Maternal history of gestational diabetes
	Severe anemia	
	Idiopathic	

greatest risk of death and disability. In preterm infants, mortality ranges from 20% to 40% and increases sharply in infants with surgical NEC and in infants with lower birthweight and lesser gestational age and may approach 100% in the smallest and least mature infants. Moreover, at all gestational ages, a history of hypotension, metabolic acidosis, thrombocytopenia, and proven bacterial sepsis correlate with a poor prognosis. (15)(21) Hence, mortality after NEC depends on factors unique to each infant, such as the need for surgery and the complications that arise from life-sustaining care. (14)(16)

PATHOPHYSIOLOGY RELATIVE TO INFANT RISK FACTORS

The pathogenic sequence in NEC is multifactorial and complex. Some researchers have proposed that the definition of NEC be individualized to include risk factors associated with the onset of disease. (22) However, this level of distinction may not be necessary, and more general themes attributed to common pathophysiologic pathways underlying NEC are proposed. For example, 3 general features underlie NEC in all infants: 1) dysbiosis, 2) injury to the intestinal lining, and 3) activation of an immune response. Dysbiosis is the abnormal balance of gut microbiota favoring opportunistic and pathogenic bacteria, or pathobionts. The other features underlying the pathogenesis of NEC include injury to the intestinal lining and activation of proinflammatory immune responses in the gut and periphery. (23)(24)(25)(26)(27) As such, factors that contribute to critical components in the pathogenic sequence can be categorized as factors that incite, promote, and permit disease (Fig 1). (14)(20) Factors that incite NEC may do so through injury to the intestinal barrier resulting from decreased bowel perfusion or after direct damage to the intestinal lining from bacterial metabolites, toxins, or infant formula feeds. Poorly digested formula or the use of antibiotic agents may then result in dysbiosis or bacterial overgrowth conditions that promote disease. (25) Finally, circumstances unique to each infant, such as prematurity, congenital heart disease, or sepsis, are factors that permit NEC to occur. These factors, taken together, result in the conditions necessary for NEC, including bacterial overgrowth, loss of bowel wall integrity, and the generation of proinflammatory immune responses triggering bacterial invasion in the gut and disease progression. (24)(28)(29)(30) Although abundant evidence supports a role for pathogens in NEC, no specific bacterium, fungus, or virus has been shown to be causative in most cases. (25)

Next-generation sequencing of stool demonstrated dysbiosis before the development of NEC. (31)(32) Pathobionts present in the microbiota of the gut in infants who develop NEC may, therefore, be "bystanders" rather than the primary cause of disease. The inflammatory cascade generated in response to bacterial overgrowth may additionally damage the epithelium, leading to increased intestinal

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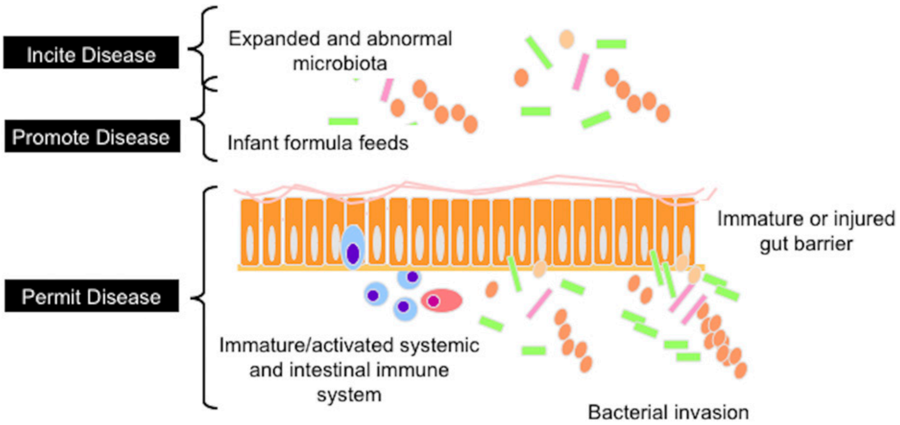
Incite Disease
Promote Disease
Expanded and abnormal microbiota
Infant formula feeds
Permit Disease
Immature or injured gut barrier
Immature/activated systemic and intestinal immune system
Bacterial invasion

Figure 1. The pathogenic sequence of necrotizing enterocolitis (NEC). Examples of factors that may incite, promote, and permit the pathogenic sequence thought to underlie NEC. (Adapted from Hunter CJ, Upperman JS, Ford HR, Camerini V. Understanding the susceptibility of the premature infant to necrotizing enterocolitis (NEC). *Pediatr Res.* 2008;63(2):117–123.)

permeability and translocation of bacteria. Furthermore, immune activation and often a systemic inflammatory response syndrome results from decreased barrier function, leading to proinflammatory cytokine–mediated injury in the brain and subsequent neurodevelopmental injury. (24)(33)

The development of NEC after red blood cell transfusion, so-called transfusion-associated NEC (TNEC), has been recognized for 2 decades, although the mechanism remains poorly understood. (34) Retrospective cohort studies highlighted the association when more than 30% of VLBW infants developed NEC within 48 hours of receiving PRBC transfusion. (9) TNEC developed in infants born at earlier gestational ages with a history of PRBC transfusion. In addition, TNEC developed at later postnatal ages than did gestational age–matched controls, with an average onset at 3 to 5 weeks of postnatal age compared with 1 to 3 weeks of postnatal age in VLBW infants with NEC unrelated to transfusion. (9)(10) One controversial risk factor for TNEC may result from increased iron handling in the intestinal epithelium in response to the recycling of effete red blood cells after transfusion. (35)(36) Other authors suggest that PRBC transfusion may not cause NEC directly but that symptomatic anemia is an independent infant risk for the development of NEC. For example, infants with transfusion-related acute gut injury had a larger degree of anemia with lower hematocrit levels. (9) Furthermore, elevated levels of intestinal fatty acid binding protein, a marker of intestinal mucosal injury, were found before and after PRBC transfusion. (36) It is, therefore, possible that anemia results in decreased oxygen delivery to the gut, rendering the mucosa at increased risk for injury associated with feeding, a state that is suddenly reversed with PRBC transfusion, resulting in a reperfusion-type mucosal gut injury. (5) Further research is needed to determine the relationships among anemia, transfusions, and NEC.

CLINICAL PRESENTATION AND DIAGNOSIS

The diagnosis of NEC is suspected from infant demographics and clinical presentation but is confirmed by the presence of pneumatosis intestinalis on abdominal radiographs. The clinical symptoms in infants later confirmed to have NEC may vary from subtle to fulminant. Infants presenting with fulminant disease may have either focal abdominal signs and symptoms or nonspecific systemic signs and symptoms with cardiorespiratory collapse indistinguishable from sepsis, metabolic disease, or critical congenital heart disease. A subtle presentation may include signs and symptoms of feeding intolerance, with gastric feeding residuals, abdominal distention, and nonspecific findings on an abdominal radiograph. Abdominal signs and symptoms may progress to include gastric feeding residuals, distention, visible loops of bowel, discoloration of the abdominal wall, or presence of tenderness on abdominal examination, accompanied by bilious gastric drainage, bloody stools, and, less commonly, emesis. Systemic signs and symptoms may include lethargy, temperature instability, new or worsening apnea, bradycardia, decreased perfusion, mottling, and hypotension. Abnormal laboratory tests often encountered in patients with NEC, although not specific to NEC alone, are the presence of thrombocytopenia, neutropenia, elevated C-reactive protein level, metabolic acidosis, electrolyte abnormalities, and coagulopathy. (1)(36) Similar to the onset of NEC, disease progression may follow a slow and stepwise deterioration, or it may be rapid in onset, with fulminant progression and death. (37)

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The Bell system was proposed nearly 40 years ago to enable uniform clinical staging stratifying infants into the categories of suspected (stage I), definite (stage II), and advanced (stage III) NEC based on clinical and radiographic findings. (38)(39) A subsequent version, modified Bell staging, included additional clinical signs and symptoms and predicted the likelihood of surgery (Table 2). (39) The signs and symptoms of suspected or stage I NEC overlap with feeding intolerance, whereas stage II NEC is defined by the presence of pneumatosis intestinalis on abdominal radiographs (Fig 2). Pneumatosis intestinalis is pathognomonic for NEC and results from intramural gas generated during anaerobic bacterial metabolism that becomes trapped in the submucosal layer of the bowel wall (Fig 3). Stage II NEC is a surgical emergency if injury progresses to full-thickness destruction of the bowel wall, leading to intestinal perforation. Intestinal perforation is visible as portal venous and free intraperitoneal air on abdominal radiography (Fig 2). Progression to stage III NEC often leads to hemodynamic instability and respiratory compromise requiring cardiorespiratory life support. Bell staging has also been shown to be useful in predicting disease outcomes as well as the likelihood of surgical intervention in NEC. For example, infants with stage II NEC are at higher risk for perforation and surgical intervention, correlating with increased morbidity and mortality. (2)(7)

Disease monitoring by clinical, laboratory, and radiographic parameters is crucial. Serial abdominal radiography is considered the gold standard to evaluate infants for disease progression. Radiography is used to determine the presence of pneumatosis intestinalis, pneumoperitoneum (free air in the abdominal cavity), or portal venous air. (1)(40) Intestinal perforation, as indicated by the presence of pneumoperitoneum, requires immediate surgical evaluation and intervention. (1)(41)(42) The radiographic appearance of abdominal free air may, however, be subtle and may become apparent in only 60% of infants with identified perforation intraoperatively. (41) Abdominal ultrasonography may be used as an adjunct to radiography in diagnosing NEC, with positive findings of pneumoperitoneum, focal fluid collection, portal venous gas, pneumatosis intestinalis, and Doppler-identified areas of bowel hypoperfusion. (1)(41)(43) However, expertise in abdominal sonography may not be widely available and is limited by observer variability. (44) Biomarkers in stool, urine, and serum to identify or confirm infants with early-stage or progressive NEC are under evaluation. Although many are appealing, such as fecal calprotectin and fatty acid binding protein in the urine, an ideal biomarker has yet to be identified, and further research is still needed. (26) Thus, having a high index of suspicion, performing serial physical examinations, and closely following the patient's laboratory studies and abdominal radiographs, remain the standard for diagnosing NEC. (37)(39)(40)(43)

DISEASE MANAGEMENT AND OUTCOMES

Most infants with NEC are managed medically, with approximately 30% progressing to surgical disease. Nearly 85% of term infants survive when diagnosed as having suspected NEC (Bell stage I) compared with 25% survival for confirmed and advanced NEC (Bell stage II or III). (20) Hence, outcomes in NEC depend on factors unique to each infant,

TABLE 2. **Modified Bell Staging in Necrotizing Enterocolitis**

BELL STAGE	CLINICAL	RADIOGRAPHIC	GASTROINTESTINAL
I	Apnea and bradycardia, temperature instability	Normal gas pattern or mild ileus	Gastric residuals, occult blood in stool, mild abdominal distention
IIA	Apnea and bradycardia, temperature instability	Ileus gas pattern with ≥1 dilated loops and focal pneumatosis	Grossly bloody stools, prominent abdominal distention, absent bowel sounds
IIB	Thrombocytopenia and mild metabolic acidosis	Widespread pneumatosis, ascites, portal venous gas	Abdominal wall edema with palpable loops and tenderness
IIIA	Mixed acidosis, oliguria, hypotension, coagulopathy	Prominent bowl loops, worsening ascites, no free air	Worsening wall edema, erythema and induration
IIIB	Shock, deterioration in laboratory values and vital signs	Pneumoperitoneum	Perforated bowel

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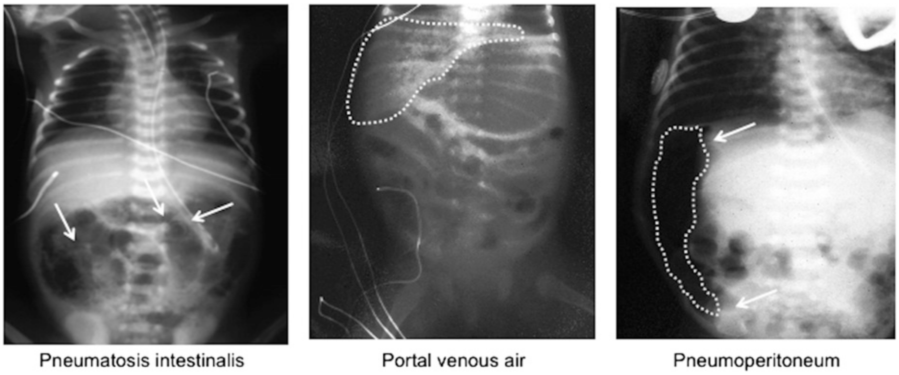

Figure 2. Radiographic appearance of necrotizing enterocolitis. Abdominal radiographic findings include pneumatosis intestinalis, visible as linear streaks (arrows) and as a "bubbly" appearance throughout the bowel; portal venous air noted throughout the liver (inside white dotted line) and dilated and stacked loops of bowel with thickened walls; and pneumoperitoneum visible as an air pocket (encircled by white dotted line and arrows) overlying the liver in the righted left lateral decubitus view.

the need for surgery, and complications arising from life-sustaining care. (14)(16) Again, it is imperative that index of suspicion for NEC in all infants remains high because early recognition of disease and treatment may lessen the severity of outcomes. (38)(40) Medical management for suspected and confirmed NEC overlap. Pediatric surgical consultation is advised in every case of suspected NEC, especially for cases with confirmed stage II NEC. Infants with suspected or confirmed NEC should be placed nil per os to allow for bowel rest. A gastric tube for bowel decompression and monitoring of aspirates should be placed. Parenteral nutrition is indicated to optimize delivery of calories during this period of bowel rest. An initial radiograph of the abdomen and a left lateral decubitus or crosstable view should be obtained to rule out evidence of free air. Serial and positional abdominal radiographs with a frequency consistent with the suspicion and cadence of advancing clinical disease should follow the initial series. A complete blood cell count with differential and platelet counts; measurement of electrolytes, arterial blood gas, lactate, and C-reactive protein; and studies to evaluate liver function and coagulation are warranted to monitor clinical disease and its progression. Correction of anemia, thrombocytopenia, electrolyte disturbances, and coagulopathy will be part of management.

Antimicrobial coverage should broadly target gram-negative and anaerobic bacteria (common gut-associated bacteria) with a duration of 7 to 14 days based on clinical suspicion, confirmation of disease, and the infant's clinical course. (1) The use of antifungal agents should be considered in severely ill patients or those who may not be responding to antibiotic drug therapy. Results of blood and, if available, peritoneal cultures will help narrow the antimicrobial coverage and guide the duration of therapy. Appropriate antibiotic drug therapy has been shown to improve the outcome and survival of infants with NEC. Infants with an advanced or rapidly progressive disease or cardiorespiratory compromise may necessitate resuscitative measures, including evaluation of airway, breathing, and

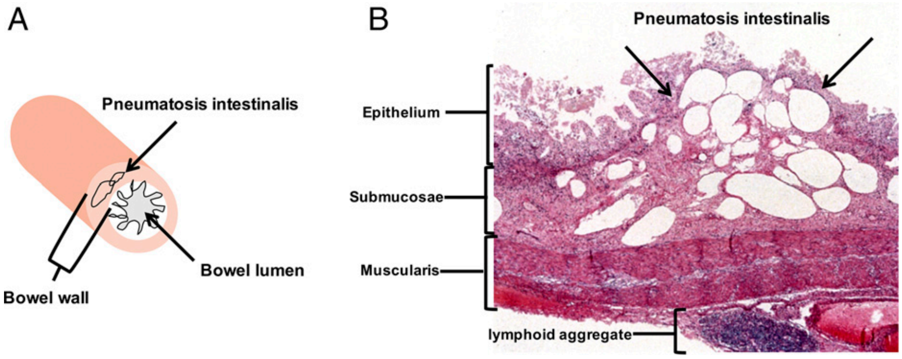

Figure 3. A. Schematic representation of the small bowel demonstrating the location of pneumatosis intestinalis in the bowel wall (arrows). B. Histologic features of necrotizing enterocolitis on a light micrograph of a segment of the small bowel stained with hematoxylin and eosin. Visible are destruction of the intestinal epithelium and villi, pneumatosis intestinalis in the submucosae and inflammatory cells distributed throughout the bowel wall, and a lymphoid aggregate/lymph node in the serosal layer.

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circulation. Infants with NEC or signs and symptoms of NEC require hospitalization in a NICU or PICU.

The development of pneumoperitoneum is an absolute indication for surgical consultation and intervention. (45)(46) In the preterm infant with pneumoperitoneum, initial management may include placement of a peritoneal drain, exploratory laparotomy, and bowel resection. (47) In some cases, the bowel is severely affected, and a second-look surgical procedure is planned weeks to months after the primary diagnosis and surgery. (48) The area and extent of bowel involvement may also differ between premature and term infants. The most commonly affected sites are the jejunum and ileum for premature neonates, whereas the colon is typically affected for infants born at term. (8)

The complications of NEC can be devastating and include acute and chronic clinical complications such as sepsis, meningitis, abdominal abscess formation, coagulopathy and associated bleeding, respiratory and cardiovascular insufficiency, metabolic complications, and later-onset neurodevelopmental injury. The outcome is significantly affected in cases of surgical NEC compared with medical NEC and in premature newborns compared with term newborns. (49)(50)(51)

Intestinal stricture formation is present in 10% to 35% of cases of NEC. (52) Strictures may affect multiple areas of the bowel, but most frequently the colon. Strictures may be diagnosed using contrast studies of the bowel or become evident because of feeding intolerance on refeeding after NEC or because of fixed and dilated loops of bowel after disease resolution. Surgical resection with end-to-end anastomosis or ostomy creation and later anastomosis are potential management approaches. Surgical treatment of NEC may result in an anatomical short bowel syndrome and intestinal failure. Indeed, NEC can be a primary cause of intestinal failure that may lead to a long-term requirement for parenteral nutrition. In severe cases of intestinal failure, intestinal transplant is the only solution. Parenteral nutrition increases the risk of growth failure, central line–associated sepsis, and total parenteral nutrition–associated liver disease. Fortunately, infants with medically treated NEC are more likely to have return of normal intestinal function and feeding tolerance.

Neurodevelopmental injury resulting in an increased incidence of cerebral palsy, cognitive and visual impairment, and neurodevelopmental delay has been described in the premature infant with NEC and in term infants with severe disease. (51)(53) A recent prospective study showed that extremely-low-birthweight survivors of NEC had an increased risk of severe neurodevelopmental disability, postdischarge surgery, and tube feeding at 18 to 24 months. Future studies are needed to assess the long-term risks of complications after NEC in late-preterm and term infants. (51)(54) Pediatricians who follow patients with a history of NEC should ensure appropriate ongoing and follow-up care for all medical, surgical, and neurodevelopmental needs. In many instances, a multidisciplinary team is necessary to provide the best outcomes from NEC.

DIFFERENTIAL DIAGNOSIS

The scope of the differential diagnosis in NEC depends on the gestational and postnatal ages of the infant, other clinical conditions and diagnoses, and the health status before the onset of symptoms. For example, in premature infants, feeding intolerance of prematurity and spontaneous intestinal perforation (SIP) should be considered. If previous patency and bowel function were noted before the development of signs of NEC, most congenital abnormalities can be ruled out, but if patency and bowel function were never established, then congenital malformations such as intestinal stenosis, meconium plug syndrome, or other functional disorders must be considered. Feeding intolerance and SIP develop in the same cohort of premature infants who develop NEC. Infants with feeding intolerance have increased pregavage residuals, mild abdominal distention, visible loops of bowel, constipation, and increased apnea, but blood studies will remain reassuring and abdominal radiographs will most likely not show abnormal findings. The feeding intolerance of prematurity, unlike the feeding intolerance of NEC, is self-limited and may be managed by a short period of withholding feeds and then a mindful, slow advancement of enteral feeds and rectal suppository use as clinically indicated. SIP affects infants with a birthweight of less than 1,000 g and usually during the first 2 weeks of life, often before the start of enteral feeds or during trophic feeding (introducing minute enteral feeds to stimulate gut maturation in preterm infants). Concurrent exposure to indomethacin and corticosteroids statistically increases the risk of SIP in infants. (55) The terminal ileum is the usual site of perforation in SIP, and on surgical exploration, there is little evidence of gross or microscopic inflammation, which distinguishes NEC from SIP. (56) The management of SIP overlaps with that of NEC and necessitates immediate gastric decompression, discontinuation of feeds, intravenous fluid hydration, antibiotic drug coverage, and prompt surgical consultation. In the first few hours to days after birth, neonates who are otherwise well-appearing but have bloody stools should be carefully evaluated for NEC. However, in the absence of predisposing risk factors (Table 1) or if there are no systemic signs or other intestinal signs of

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injury, swallowed maternal blood during delivery, the presence of anal fissures, or allergic colitis should be considered. (57)(58)(59) The Apt test (hemoglobin alkaline denaturation test) may be used to determine the presence of maternal versus fetal blood. Maternal red blood cells are lysed under the assay's conditions, whereas fetal cells are not. (58)(60) Once swallowed maternal blood is confirmed as the source of the neonate's bloody specimen, no further intervention is needed. The presence of anal fissures is another common etiology for rectal bleeding in infants; therefore, a complete physical examination with close inspection of the perineum and anal mucosa should be performed. Application of skin barrier creams, such as petrolatum, will hasten healing of anal mucosal injury. (60) The development of cow milk protein allergy after exposure to cow milk–based formula or human milk fortified with bovine-based fortifiers may mimic the clinical presentation of NEC. Infants with this disease rarely present before 6 weeks of age. Common findings are abdominal distention, diarrhea with bloody stools, and, if severe, the presence of pneumatosis. Bowel rest and the use of elemental formula on refeeding may afford resolution of symptoms. (57)

Intestinal obstruction from atresia, intestinal duplications, malrotation with volvulus, meconium ileus, or intussusception may present similarly to NEC. Visible loops of bowel, abdominal distention, tenderness, failure to pass stool, or vomiting are often presenting signs. (36) Unlike NEC, congenital intestinal atresia or malrotation with midgut volvulus often show persistently dilated proximal and gasless bowel loops on abdominal radiographs with bilious emesis or gastric residuals. Infants with NEC are likely to show symmetrical distention with evidence of thickened loops of bowel (Fig 2). If abdominal radiographs or clinical presentation are equivocal, an upper gastrointestinal contrast study with small bowel follow-through or a lower gastrointestinal contrast enema may be recommended (water-soluble contrast if perforation is suspected). Additional consultation with radiology, pediatric surgery, and gastroenterology will enable the practitioner to refine the diagnostic approach and management strategy.

PREVENTION

Because NEC is a devastating disease, prevention and reducing the incidence are essential. Prevention of severe anemia with strategies such as delayed cord clamping if appropriate at birth and judicious blood sampling should be considered. The American Academy of Pediatrics endorsed the American College of Obstetricians and Gynecologists Committee on Obstetric Practice (61) in its recommendation of delayed cord clamping for 30 to 60 seconds after birth in vigorous term and preterm infants, which may help reduce the incidence of NEC. Other strategies to reduce NEC include limiting medications that reduce gastric acidity, especially in the preterm infant. For example, the use of histamine 2 antagonists alters the gut microbiota and may predispose the premature gut to the development of NEC. Similarly, antibiotic stewardship is an important effort to limit the risk of altering the microbiota of the intestine and other body sites, therefore likely decreasing the risk of NEC. (5)

The introduction of standardized feeding guidelines has been shown to be protective against the development of NEC. A recent systematic review including 15 observational studies demonstrated that having a standardized feeding guideline significantly reduced the incidence of NEC even when guidelines differed among NICUs. (62) A Cochrane review showed that there was no difference in NEC between NICUs that practice slower daily feed advancements (15–20 mL/kg per day) compared with NICUs that provide faster daily increments (30–40 mL/kg per day). (63) Generally, feeding guidelines initiate early minimal enteral feeds of less than or equal to 20 mL/kg per day of enteral nutrition and advance daily based on individual infant feeding tolerance. (5)(64) Regarding feeding anemic infants around a PRBC transfusion, at this time there are no clear guidelines, but current practice is to implement guidelines for enteral feeding as well as avoiding severe anemia, which may increase the likelihood of TNEC. (5)(65)

Of greater importance, however, is the role of human milk in the prevention of NEC. Human milk has been known for decades to reduce the incidence of NEC and bacteremia compared with infants fed formula, at least as far as premature and low-birthweight infants are concerned. If the mother's milk is not available, pasteurized donor human milk has also been shown to decrease the risk of NEC, despite the known effects of pasteurization on the immune, antimicrobial, barrier-enhancing, and regenerative components in human milk. (30)(66) Indeed, the only known consistent intervention in the prevention of NEC is human milk. (12)(30)(67)(68)(69) However, the caloric requirements to maintain the fetal growth trajectory after birth in VLBW infants are not met with native human milk, thereby requiring milk fortification to meet the nutritional needs of these infants. (70)(71) More recently, randomized clinical trials have shown that an exclusive human milk diet consisting of human milk fortified with a human milk–derived fortifier (rather than a bovine-based fortifier) further decreased the rate of NEC and, more specifically, surgical NEC, (67)(69) as well as decreasing other outcomes,

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including sepsis, days of parenteral nutrition, and death. (72) The American Academy of Pediatrics supports human milk as optimal nutrition for all neonates and supports its use as a protective strategy for preterm infants in the prevention of NEC. (73)(74)(75) Similarly, as in preterm infants, if the mother's milk is not available, pasteurized donor human milk, which has been shown to decrease the risk of NEC, should be considered in term infants as well. (30)(66)

Relative abundances of certain human milk oligosaccharides have been shown to correlate with protection from NEC and to exert a protective effect. (76)(77) A prospective multicenter study of preterm infants found an almost 10-fold increase in the incidence of NEC in formula-fed infants compared with human milk–fed infants. Both observational and randomized studies demonstrate that formula-fed preterm infants have an increased risk of NEC compared with those fed human milk, although whether this association holds for term infants and those with congenital or chromosomal abnormalities remains an area in need of greater study. (6)(19)(68)(78) In any case, the positive effects of human milk are due to the wide array of antimicrobial and immune and regenerative factors present in human milk, including secretory immunoglobulin A, other immunoglobulins, oligosaccharides, lactoferrin, anti-inflammatory cytokines, and growth factors. (79) In addition, freshly expressed mother's milk provides commensal flora, which results in colonization by beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* species thought to have multiple effects on microbial homeostasis and immune and gut maturation. (27)

A meta-analysis was performed with 20 randomized controlled trials using *Bifidobacterium* and *Lactobacillus* species probiotics in the prevention of NEC. Probiotic supplementation with either probiotic or a combination of both significantly decreased the risk of NEC and death in preterm VLBW infants, without an increased risk of sepsis between the probiotic and placebo groups. (80) Term infants consuming formula supplemented with a single oligosaccharide, 2'-fucosyllactose, had increased *Bifidobacterium* species and decreased pathogenic bacteria in the microbiota of the stool. Also, the systemic cytokine profile of these infants was more like that of breastfed control infants. (81)(82) However, the vast array of human milk oligosaccharides naturally occurring in human milk coupled with other antimicrobial and immune and regenerative factors present in human milk argue that human milk feeding should remain the primary nutrition for these infants. (77) Despite promising results from multiple trials, the use of probiotics and prebiotics is not routine in the prevention of NEC in clinical practice. (83) In the United States, this may be due to the lack of an approved drug (rather than the availability of products as over-the-counter nutritional supplements), product variability, unestablished dosing regimens, and variability in trial outcomes due to differences in clinical trial design. (82)(83)

Summary

- The incidence of necrotizing enterocolitis (NEC) in preterm infants has decreased during the past several decades.
- Strong evidence supports that human milk feeding and the avoidance of bovine-based infant formulas have had the greatest protective effect in preterm and low-birthweight infants. (12)(30)(67)(69)
- Multiple observational studies (8)(13)(16)(18)(20) and, more recently, a large retrospective study (19) demonstrate that NEC is proportionally increased in infants with congenital anomalies such as gastroschisis and congenital heart disease.
- Short- and long-term complications of NEC are devastating in all infants.
- Once NEC is diagnosed and/or strongly suspected, a pediatric surgical consultation and a management plan are warranted.
- Consistent practitioner guidelines for feeding, prioritizing the use of human milk, avoidance of severe anemia, and limiting medications that may alter gut microbiome should be considered standard approaches for the prevention of NEC.

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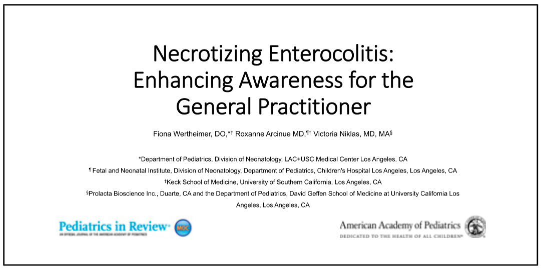

Necrotizing Enterocolitis:
Enhancing Awareness for the
General Practitioner

Fiona Wertheimer, DO,*† Roxanne Arcinue MD,¶† Victoria Niklas, MD, MA§

*Department of Pediatrics, Division of Neonatology, LAC+USC Medical Center Los Angeles, CA
¶Fetal and Neonatal Institute, Division of Neonatology, Department of Pediatrics, Children's Hospital Los Angeles, Los Angeles, CA
†Keck School of Medicine, University of Southern California, Los Angeles, CA
§Prolacta Bioscience Inc., Duarte, CA and the Department of Pediatrics, David Geffen School of Medicine at University California Los Angeles, Los Angeles, CA

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1. You are caring for a term infant boy who has hypoplastic left heart syndrome. He had surgery with a Norwood procedure. Two days after surgery, low-volume feedings were initiated with human milk. Five days after surgery, he developed feeding intolerance, abdominal distention, and decreased blood pressure. His abdominal radiograph shows several dilated loops of bowel with small focal segments of pneumatosis. You diagnose necrotizing enterocolitis (NEC). Which of the following is the most likely underlying etiology for this infant's presentation with NEC?
    A. Bowel malrotation.
    B. Bowel perforation.
    C. Decreased perfusion to the gut.
    D. Need for revision of the Norwood procedure.
    E. Reaction to human milk.
2. A 20-day-old infant girl is delivered at 32 weeks' gestation because her mother had a stroke related to hypertension. Feedings are initiated with formula owing to the mother's severe illness. The infant develops bilious emesis and abdominal distention. An abdominal radiograph is ordered. Which of the following radiographic findings is the most pathognomonic for a diagnosis of NEC in this patient?
    A. Focal fluid collection in the left lower quadrant.
    B. Gasless bowel loops.
    C. Markedly dilated loops of proximal bowel.
    D. Nonspecific bowel gas pattern.
    E. Pneumatosis intestinalis.
3. A 14-day-old boy born at 30 weeks' gestation has increasing residuals noted with his feedings. Feedings with human milk were initiated 11 days ago. He has mild abdominal distention, temperature instability, and increasing frequency of apnea spells. His abdominal radiograph is nonspecific. Which of the following is the most appropriate next step in the management in this patient?
    A. Immediate intubation.
    B. Liver biopsy.
    C. Microbiome analysis.
    D. Serial abdominal radiographs.
    E. Surgical consultation.
4. You are caring for a term infant girl who has abdominal distention and vomiting. She is not passing stool. Your differential diagnosis includes malrotation with midgut volvulus, congenital intestinal atresia, and NEC. Which of the following findings on abdominal radiography is most likely to be concerning for NEC?
    A. Absence of air in the bowel.
    B. Evidence of stool throughout the bowel.
    C. Lack of rectal stool.
    D. Proximal dilated gasless bowel loops.
    E. Symmetrical distention with thickened loops of bowel.

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5. You are working on a committee for your hospital focused on preventing NEC in infants in the nursery. Which of the following is the most effective measure to advocate for to achieve this goal?
   - A. Delayed cord clamping for 30 to 60 seconds after birth in vigorous infants.
   - B. Early introduction of hypoallergenic formula feedings.
   - C. Prescription of probiotics for all infants.
   - D. Prophylactic antibiotic drug treatment of infants at risk for NEC.
   - E. Prophylactic use of histamine 2 antagonists.

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Index of Suspicion

1 Sudden Bilateral Lower Extremity Weakness and Urinary Incontinence in a 13-year-old Girl

Raymond Cai, MD,* Vikram Bhise, MD†

*Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ
†Department Neurology and Pediatrics, Robert Wood Johnson University Hospital, New Brunswick, NJ

EDITOR'S NOTE

I spent a week with medical students and family medicine residents in northeast Africa earlier this year. There, bright, clinically astute trainees at a major university use *Pediatrics in Review* as a core foundation of their pediatric curriculum. Wherever you are in the world this month, may these *Index of Suspicion* cases help you advance your knowledge and practice of pediatrics.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A 13-year-old girl presented to the emergency department with acute onset of lower extremity weakness. She first awoke with dizziness but soon developed severe back pain, bilateral lower extremity pain and numbness, slurred speech, and inability to move her lower extremities or ambulate.

She reports having a 2-day history of headaches and back pain. Due to worsening of her symptoms, she went to an urgent care center the previous day. A rapid viral test showed she was influenza positive, and she took 2 doses of oseltamivir before admission. The patient had an upper respiratory tract infection approximately 2 to 3 weeks ago. In the emergency department, the patient is unable to void spontaneously despite being able to at home, and a urinary catheter is placed.

On physical examination her vital signs are as follows: temperature, 98.6°F (37.0°C); heart rate, 77 beats/min; respiratory rate, 20 breaths/min; and blood pressure, 119/74 mm Hg. Her BMI was within the 75th to 85th percentile. Her lower extremities bilaterally had 1/5 strength, diminished sensation to pinprick and temperature, and 0/5 patellar reflexes. She also had a 0/5 right Achilles reflex but a 1/5 left Achilles reflex. Her upper extremity strength, sensation, and reflexes were intact. Examination of her back showed no spinal tenderness to palpation or erythema. The rest of the physical examination findings were normal. Initial laboratory findings were normal, including complete blood cell count, complete metabolic panel, C-reactive protein level, creatine phosphokinase level, lactate level, and urinalysis. Polymerase chain reaction for common upper respiratory tract infection pathogens as well as cerebrospinal fluid (CSF) cultures were negative. CSF studies showed a white blood cell (WBC) count of 1/μL (0.001×10^9/L), a red blood cell count of $0\times10^6/\mu$L (0×10^{12}/L), a protein level of 0.015 g/dL (0.15

AUTHOR DISCLOSURE Drs Cai and Bhise have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Cai's current affiliation is Children's Hospital at Montefiore, The Bronx, NY.

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g/L), and a glucose level of 53 mg/dL (2.9 mmol/L). Magnetic resonance imaging (MRI) of her brain and spinal cord with contrast was normal.

DISCUSSION

Despite the normal CSF findings, there was concern for a treatable condition such as Guillain-Barré syndrome, so intravenous immunoglobulin (IVIG) was initiated for 5 days. Electromyography (EMG) with nerve conduction studies (NCSs) was performed and demonstrated normal motor and sensory unit action potentials with normal latencies, amplitudes, and conduction velocities but significantly reduced recruitment of motor unit action potentials (MUAPs) bilaterally, worse on the right leg. This indicated a possible demyelinating motor neuropathy, and a regimen of 1 g of methylprednisolone daily for 5 days was added. Subsequent examinations demonstrated mixed upper (UMN) and lower (LMN) motor neuron findings. Her bilateral diminished lower extremity strength and sensation improved dramatically, left slightly more than right. Her right patellar and left Achilles reflexes became brisk, and her left patellar and right Achilles reflexes remained absent. She also developed crossed adductor reflexes and a positive left Babinski sign. The absent or diminished reflexes in the left patella and right Achilles indicated an LMN process, and the brisk reflexes in the right patella and right ankle, crossed adductor reflexes, and positive Babinski sign indicated a UMN process. The patient's muscle tone was consistently normal. Repeated MRI studies 3 days after admission demonstrated new spinal cord lesions spanning from T6-7 down to the conus medullaris (Fig 1) with bilateral symmetrical T2 signal changes limited to the anterior gray matter (Fig 2).

Findings from further infectious, autoimmune, and metabolic evaluation were also negative or normal: serum human immunodeficiency virus, Epstein-Barr virus and CSF enterovirus, mycoplasma, and herpes simplex virus polymerase chain reaction; antinuclear antibodies, anti–double-stranded DNA, anti–SS-B, anti–myelin oligodendrocyte glycoprotein, and Lyme antibodies; CSF oligoclonal bands and immunoglobulin G index; serum vitamins B_{12}, D, and E; biotinidase; erythrocyte sedimentation rate; copper; and zinc. Test results were positive (after IVIG treatment) for anti–SS-A, human T-lymphotropic virus types 1 and 2, and mycoplasma immunoglobulin G antibodies.

DIFFERENTIAL DIAGNOSES

Possible conditions that the patient could have experienced can be split into 2 categories (1): peripheral (acute polyneuropathy, acute radiculoneuropathy [eg, Guillain-Barré], acute anterior poliomyelitis, acute flaccid myelitis) and central (acute transverse myelitis, acute flaccid myelitis, multiple sclerosis, neuromyelitis optica, subacute combined degeneration of the spinal cord, Wilson disease, infectious myelitis, cauda equina syndrome, lumbosacral neuritis, spinal stroke).

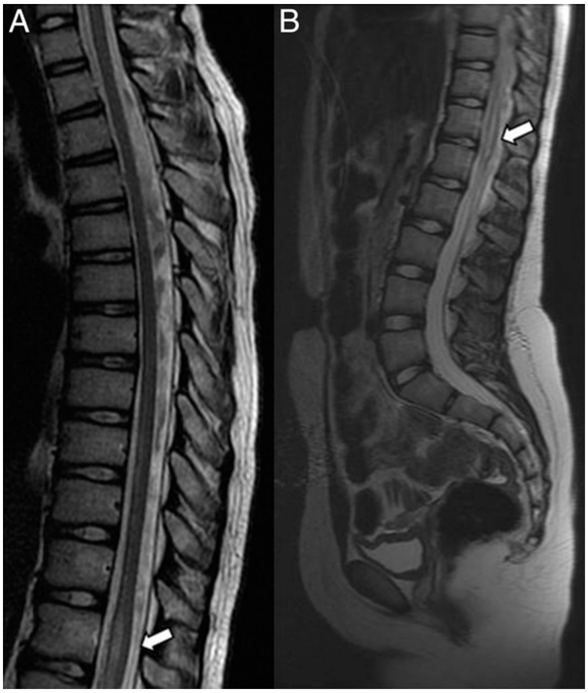

Figure 1. Sagittal view of the spinal cord with T2-weighted images showing the abnormal T2 signal spanning from T6-7 down to the conus medullaris (arrows). A. T2 weighted sagittal image of the patient's mid-clavicular to mid-lumbar spinal cord. B. T2 weighted sagittal image of the patient's mid-lumbar to sacral spinal cord.

THE CONDITION

Acute flaccid myelitis (AFM) is a rare neurologic disease of unknown etiology. Despite numerous studies implicating enterovirus-68 (EV-68) and other polioviruses as the cause, none have been definitively established to date. Currently, the Centers for Disease Control and Prevention (CDC) defines a confirmed case of AFM as having 1) acute onset of focal limb weakness *and* 2) an MRI showing a spinal cord lesion largely restricted to gray matter spanning 1 or more spinal segments. A probable case of AFM has 1) acute onset of focal limb weakness *and* 2) CSF with pleocytosis (adjusted WBC count $>5/\mu L$ [$>0.005\times10^9/L$]). (2)

This disease mostly affects children and adolescents who present with poliolike symptoms. (3) It can be preceded by a prodromal febrile illness with respiratory and gastrointestinal symptoms a few days in advance. (3)(4) The most

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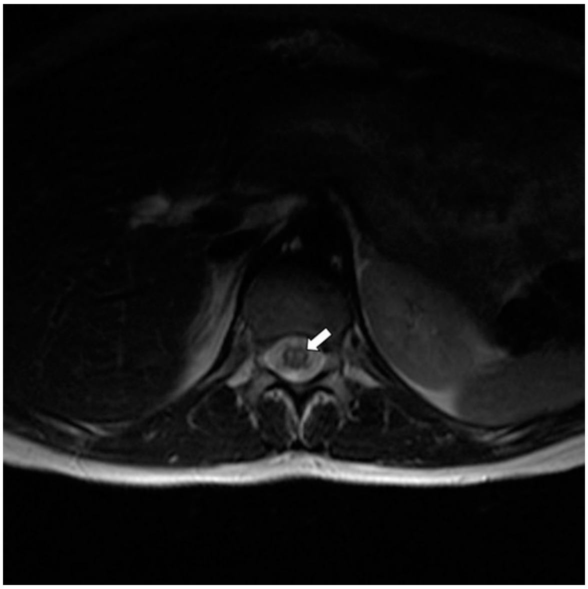

Figure 2. Tranverse view of the spinal cord with a T2-weighted image showing abnormal T2 signals localized in the bilateral anterior horn cells (arrow).

common respiratory symptoms include rhinorrhea, cough, and sore throat, and the most common gastrointestinal symptoms are vomiting or diarrhea. (5)(6) During the acute phase of the disease, patients mostly complain of fever, headache, neck pain, or pain around the affected limb. (3)(4) Neurologic findings include upper or lower limb weakness, sensory deficits, bladder or bowel dysfunction, hyporeflexia in the flaccid limbs, and varied cranial nerve dysfunction. (3)(4)(5)(6) Limb involvement includes 1 to all 4 extremities, more commonly the upper extremities, in an asymmetrical manner, with weakness ranging from paralysis to mild weakness. (3)(5)(6) The progression of neurologic symptoms can occur quickly, from a few hours to a few days. (6)(7)

Diagnostic studies such as MRI, lumbar puncture, and NCS/EMG can provide further evidence of the disease. MRI of the brain and spine reveals abnormal T2 signals localized to the anterior horn cells of the spinal cord correlating to the neurologic symptoms. These lesions can occur throughout the spine as well as in the dorsal pons and medulla. (8) Early MRIs of the spinal cord may be normal, and repeated imaging is required. (6)(7)(8) Early imaging may also show lesions throughout the gray matter that may be accompanied by edema. (8) Because the disease targets the anterior horn cells of the spinal cord, patients typically have LMN findings, but surrounding inflammation in the spinal cord leads to concomitant UMN findings. Analysis of the CSF often showed pleocytosis with a lymphocytic predominance. Although pleocytosis was not found in our patient, various case reports and reviews found the median WBC count to be approximately 43 to 44/μL (0.04×10^9/L), but the CDC notes a higher median count of 163/μL (0.16×10^9/L). (5)(6)(9)(10) Studies also found elevated CSF protein levels (>45 mg/dL [>450 g/L]; reference range, 15–45 mg/dL [150–450 g/L]) but normal glucose levels (reference range, 40–80 mg/dL [2.2–4.4 mmol/L]) in most patients. (5)(6)(9)(10) NCS/EMG performed in multiple case reports and series noted reduced compound MUAP amplitudes, recruitment of MUAPs, and denervation of affected muscles. (6)(11)(12) One study found that despite the decrease in MUAPs, sensory unit action potentials were unchanged. (11) Fibrillation potentials started appearing 1 week after the onset of symptoms. (6) These abnormal NCS/EMG findings persisted for months (>20 weeks). (6)

The presence of UMN and LMN symptoms, the characteristic MRI appearance, and the NCS/EMG findings led us to the diagnosis in this patient.

MANAGEMENT

Management of AFM is mainly supportive, but the patient's respiratory status must be monitored carefully. Cervical lesions can lead to respiratory distress, and various case series have reported patients having respiratory insufficiency requiring intubation. (4)(5)(6)(9)

No formal guidelines have been established to acutely treat AFM, but multiple case reports and series have used various combinations of IVIG, high-dose intravenous corticosteroids, and/or plasma exchange to treat patients to various levels of improvement. (5)(6)(9)(10) There is no clear evidence or studies performed that prove that those therapies are either harmful or helpful for AFM treatment. (4) Furthermore, because of the unknown pathophysiology of the disease, the role of those therapies remains unclear. Corticosteroids are indicated for cord edema; however, it may worsen an active infectious process. (3)(4) IVIG is considered safe to use in most patients. Neutralizing antibodies against EV-68 have been found in commercially prepared IVIG. (4)(13) Plasma exchange can theoretically remove protective antibodies, which could worsen the disease process. (4) Fluoxetine has also been examined as a therapy for its antiviral effects against EV-68. (14) For long-term treatment, patients require physical and occupational therapy. Currently, the CDC is collecting CSF, blood, stool, and respiratory specimens from patients with possible AFM to search for potential causes.

The prognosis of this disease is variable. One study with median follow-up of 6 months found that all the children in the study had improved neurologic outcomes. All but 1 of the children still had residual motor deficits such as weakness, difficulty ambulating, and persistent need for a

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ventilator. (7) Another study with follow-up of 1.5 to 3.0 months after discharge found that all the children had improved neurologic signs. Five of 9 patients had mild to no residual deficits, and the others still had deficits, including residual limb weakness. (10) In the case series examining the nationwide outbreak of AFM in 2014 (median follow-up, 4.2 months), 5% of patients reported complete recovery of strength and 18% were fully functional. Fourteen percent of patients were reported to be completely dependent on their caregivers. (9)

PATIENT COURSE

During her hospital stay, follow-up examinations demonstrated significant improvement in her lower extremity strength and sensation, return of specific reflexes, and resolution of urinary incontinence. The patient showed improvement during the IVIG infusion, but less so during the glucocorticoid treatment. The patient was transferred to an inpatient pediatric rehabilitation center for intensive physical and occupational therapy. At her latest outpatient evaluation, the patient was ambulatory with assistance.

Lessons for the Clinician

- Acute flaccid myelitis (AFM) is a rare poliolike neurologic disease of unknown etiology that typically has a prodromal period and presents as asymmetrical weakness of 1 to 4 limbs among other neurologic findings.
- Early magnetic resonance imaging (MRI) of the spinal cord may be normal, but repeated MRI shows abnormal T2 signals in the anterior horn cells in the spinal cord.
- Patients with acute AFM should have their respiratory status monitored closely in case of respiratory compromise.
- Although there is no evidence in terms of efficacy, case series have reported the use of intravenous immunoglobulin (IVIG), intravenous corticosteroids, and plasmapheresis. IVIG is considered a safe option.
- Cerebrospinal fluid, blood, stool, and respiratory samples from patients with possible AFM should be sent to the Centers for Disease Control and Prevention for further analysis and the local department of health contacted.

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Case 1: Sudden Bilateral Lower Extremity Weakness and Urinary Incontinence in a 13-year-old Girl

Raymond Cai and Vikram Bhise

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2 Agitation and Abnormal Movements in a 14-year-old Boy

Chetna K. Pande, MD, MPH,* Amanda O'Halloran, MD,*
Rosalyn W. Stewart, MD, MS, MBA,* Angela Nguyen, MD,*
Therese Canares, MD*

**Department of Pediatrics, The Johns Hopkins Hospital, Baltimore, MD*

PRESENTATION

A 14-year-old boy with attention-deficit/hyperactivity disorder, depression, autism spectrum disorder, and astrocytoma (status-post resection in infancy, no residual deficits) presents to the emergency department (ED) with 2 days of abnormal movements: facial twitching, jaw stiffness, and torticollis, progressing to whole-body tremors, agitation, diaphoresis, and altered mental status. Medications include fluoxetine 60 mg daily and lisdexamfetamine 60 mg daily, started 1 year ago. He recently gained independence with taking medications but took no medications in the past week. Two days ago his mother discovered his noncompliance and restarted his medications at the prescribed doses. Since symptom onset, he was seen in community EDs twice, received diphenhydramine for dystonia and lorazepam for agitation, and was discharged.

Vital signs are temperature, 98.8°F (37.1°C); blood pressure, 121 to 149/64 to 76 mm Hg; heart rate, 70 to 90 beats/min, with episodes of 170 beats/min when tremulous; respirations, 18 to 24 breaths/min; and oxygen saturation, 97% to 99% on room air. He is diaphoretic and agitated; his eyes are closed, but he opens them on command. He responds to questions verbally and follows commands. He has rotary and horizontal nystagmus, right-sided torticollis, and brisk reflexes. He has episodes of bilateral lower extremity hypertonia and tremors lasting 15 to 30 seconds, up to 5 episodes per hour. His Glasgow Coma Scale score is 14 (–1 for eyes).

An electrocardiogram shows normal sinus rhythm. Laboratory results include a white blood cell count of 5,840/μL (5.84×10^9/L), a hemoglobin level of 13.1 g/dL (131 g/L), a platelet count of 239×10^3/μL (239×10^9/L), a lactate level of 12.61 mg/dL (1.4 mmol/L), and a creatine kinase level of 91 U/L (1.52 μkat/L). Head computed tomography shows no acute intracranial abnormality and unchanged postoperative findings. A clinical diagnosis is made.

DISCUSSION

Hospital Course

Our patient's constellation of symptoms, diaphoresis, intermittent tachycardia with tremors, hypertension, hyperreflexia, right-sided abnormal movements, and

AUTHOR DISCLOSURE Drs Pande, O'Halloran, and Nguyen have disclosed no financial relationships relevant to this article. Dr Stewart has disclosed that she is the project director for a Health Resources and Services Administration grant to improve health-care delivery for people with sickle cell disease. Dr Canares has disclosed that she is a grant recipient for a research project involving offering dental screenings and preventive services through the joint collaboration of the Johns Hopkins–Walgreens Committee. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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rotary nystagmus (later identified as ocular clonus), in addition to history of exposure to a selective serotonin reuptake inhibitor plus lisdexamfetamine (which has serotonergic activity), prompted a diagnosis of serotonin syndrome. His symptoms met the Hunter Serotonin Toxicity Criteria for a case of mild to moderate serotonin syndrome (Fig). (1) He received 4 mg of oral cyproheptadine, and within 30 minutes he had resolution of episodic tremors, diaphoresis, ocular clonus, tachycardia, and hypertension but had no improvement in mental status (persistent eye-opening and speech in response to verbal stimuli, but not spontaneously). Due to ongoing mental status changes, the Poison Control Center advised administering cyproheptadine 2 mg every 2 hours, as needed. He received 2 mg of oral cyproheptadine 2 hours after the first dose and subsequently became more difficult to arouse (eye-opening and speech to painful stimuli), although his tremors, clonus, and vital sign abnormalities continued to improve. Given that the rest of his examination findings substantially improved after administration of cyproheptadine, it is thought that his increased sleepiness was an expected adverse effect from the anticholinergic properties of cyproheptadine. He was admitted to the hospital for management of serotonin syndrome.

During his admission, cyproheptadine administration was discontinued. His symptoms gradually improved over 36 to 48 hours with supportive care, his neurologic and mental status examinations returned to baseline, and he was discharged 48 hours after admission. The remainder of the evaluation findings, including brain magnetic resonance imaging and electroencephalography, were normal. Psychiatry advised holding all psychiatric medications until the next outpatient appointment.

Background

Serotonin syndrome is defined as the triad of acute altered mental status, autonomic instability, and neuromuscular abnormalities associated with the initiation or increase in dosage of a serotonergic agent. (2) Symptoms can last for days after serotonin syndrome onset. Classically, serotonin syndrome is thought to develop in patients after an increased dose or overdose of serotonergic agents. However, it is important to recognize that its presentation may be unpredictable because it can occur with therapeutic dosing. (2)(3) Furthermore, exposure to lisdexamfetamine, which has an affinity for the serotonin receptor, is reported as a risk factor for serotonin syndrome. (4)(5) The spectrum of clinical manifestations is mediated by excessive stimulation

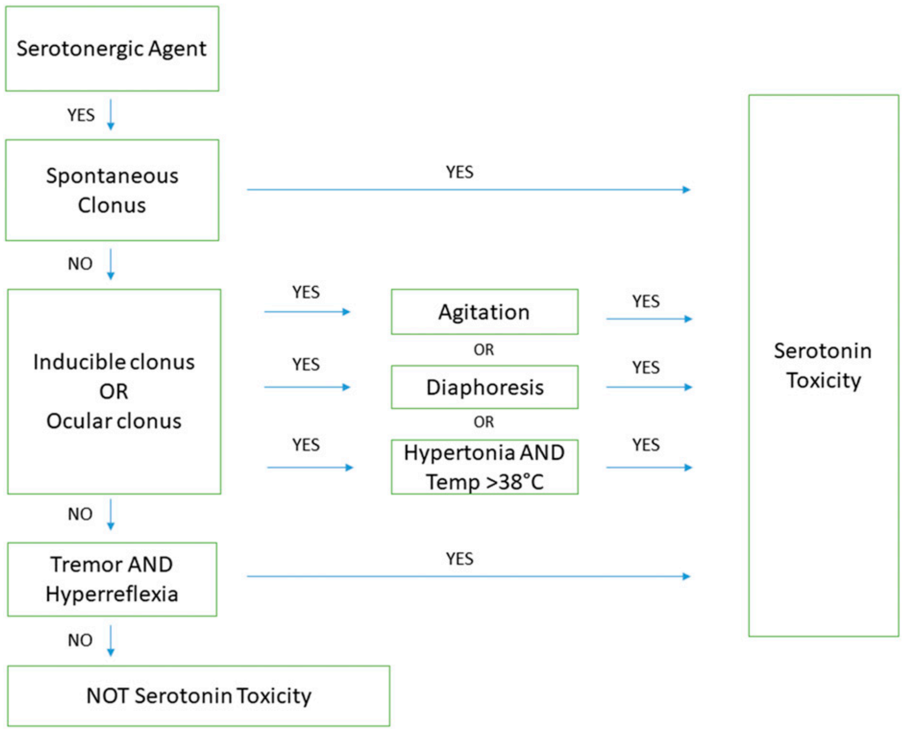

Figure. The Hunter Serotonin Toxicity Criteria. (Adapted with permission from Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM.* 2003;96(9):639.)

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of central and peripheral serotonin receptors, ranging from barely perceptible to lethal. (2)(6)

Differential Diagnosis

The differential diagnosis in the patient with neurologic or mental status changes and elevated temperature, heart rate, or blood pressure includes anticholinergic syndrome, malignant hyperthermia, and neuroleptic malignant syndrome. These diagnoses can be differentiated by a thorough history and physical examination. (7) Laboratory tests or diagnostic imaging should be used to rule out diagnoses with similar symptoms. (7) Diagnosis of serotonin syndrome may be difficult due to the variability of clinical symptoms and the potentially indolent course of the syndrome, leading patients to seek delayed care. (8)(9) Furthermore, pediatric physicians may not immediately recognize the constellation of symptoms because it is more frequently reported in adults. (8)(10)

Treatment

The mainstay of therapy for serotonin syndrome is removal of the offending serotonergic drugs and supportive care. (7)(10) Most serotonergic drugs are metabolized to their active metabolite in the liver and are renally cleared. (11) Mild cases of serotonin syndrome may resolve within 24 to 72 hours with discontinuation of offending drugs and supportive care; however, symptoms may persist for longer in patients taking drugs with longer half-lives. Mild cases may be observed in the ED for 4 to 6 hours or may require a 12- to 24-hour admission, until mental status, vital signs, and neurologic symptoms resolve. Moderate to severe cases with hyperthermia, autonomic instability, or progressive cognitive changes require hospitalization. (2)(7) Treatment should focus on management of airway, breathing, and circulation. Fluids for correction of vital signs are used, as well as benzodiazepines for control of agitation and tremors. (12) Cyproheptadine is the recommended antidote to serotonin syndrome. Cyproheptadine is an histamine-1 receptor antagonist and has antagonistic properties to the serotonin receptors 5-HT1A and 5-HT2A. (13) Strong evidence of its efficacy in serotonin syndrome is lacking because the literature is limited to case series. (7)(10) Expected adverse effects of cyproheptadine include hypotension and sedation. (13) In severe cases, hyperthermia (temperature >106°F [>41.1°C]) due to excessive muscle contractions should be treated with sedation, neuromuscular paralysis, and endotracheal intubation. (2)(14) There is no role for antipyretic agents because the hyperthermia is due to increased muscular activity and not a change in the hypothalamic set point. (2)(15) Furthermore, physical restraints should be avoided in agitation because muscle contractions can exacerbate hyperthermia. (14)

In summary, this case highlights a classic presentation of an uncommon diagnosis of serotonin syndrome in an adolescent who abruptly stopped and restarted his fluoxetine and lisdexamfetamine. His symptoms significantly improved after administration of a single dose of cyproheptadine, adding to the limited body of literature of the efficacy of this antidotal agent. Clinicians must maintain an index of suspicion for serotonin syndrome in the patient with tremor, agitation, diaphoresis, and exposure to selective serotonin reuptake inhibitors and amphetamines.

Lessons for the Clinician

- Prescribers of antidepressants and amphetamines must provide their patients with specific anticipatory guidance regarding the risks of abruptly discontinuing and restarting these medications.
- Medication compliance should be monitored closely in patients who are at risk for taking their medications erratically, such as adolescent patients.
- It is critical to maintain a high index of suspicion for serotonin syndrome in all patients with unexplained altered mental status who have a history of selective serotonin reuptake inhibitor and amphetamine exposure.
- Although evidence of cyproheptadine therapy is lacking, this case demonstrates its efficacy in an adolescent patient.

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Case 2: Agitation and Abnormal Movements in a 14-year-old Boy

Chetna K. Pande, Amanda O'Halloran, Rosalyn W. Stewart, Angela Nguyen and Therese Canares

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Index of Suspicion

3 Unexpected Diagnosis in a Febrile Infant

Jacob Kolker, MD,[*] Kathryn Halyko, MD,[†] Cody Tigges, DO[†]

[*]Department of Pediatrics, Wayne State University, Detroit, MI
[†]Stead Family Department of Pediatrics, University of Iowa, Iowa City, IA

PRESENTATION

A 34-day-old white boy presents to the emergency department with a fever (101.8° F [38.8°C]) and a 1-day history of poor feeding and fussiness. There is no other history of acute illness, although his older brother currently has oral ulcers secondary to a viral illness. He was born at term after an uncomplicated pregnancy. Maternal prenatal infection screening, including group B *Streptococcus,* was negative. He was discharged on the second day after birth and had been breastfeeding with good weight gain until the day before admission. Vascular access is obtained, a sepsis evaluation is initiated, and he is treated empirically with ampicillin, cefepime, and acyclovir.

He is admitted to the PICU due to concern for sepsis, where on examination he is awake, alert, and crying. The anterior fontanelle is soft and flat, the tympanic membranes are normal, and the oral mucosa appears pink and moist without lesions. Neurologic examination demonstrates normal tone and strength, and there are no focal deficits. The remainder of the physical examination findings are normal.

Laboratory studies are significant for a white blood cell count of 2,800/μL (2.8×10^9/L), with an absolute neutrophil count of 180/μL (0.18×10^9/L). Results of cerebrospinal fluid (CSF) studies show a total protein level of 0.118 g/dL (1.18 g/L), glucose level of 56 mg/dL (3.1 mmol/L), white blood cell count of 13/μL (0.013×10^9/L), and red blood cell count of 0.052×10^6/μL (0.052×10^{12}/L). The Gram-stain showed no organisms. Herpes simplex and enterovirus polymerase chain reaction (PCR) results are negative. The remainder of the laboratory findings, including basic metabolic panel, respiratory viral panel, C-reactive protein level, and chest radiograph, are normal.

DISCUSSION

While in the PICU the patient remained afebrile, and his fussiness and enteral intake returned to baseline. On the second hospital day we were notified that our laboratory had been testing a new PCR test awaiting Food and Drug Administration (FDA) approval, which they had run on our patient's CSF sample. They reported that his sample was positive for parechovirus. Although parechovirus is well described in the literature and well-known among pediatric infectious disease specialists, it is less familiar to general pediatricians and other pediatric subspecialists.

AUTHOR DISCLOSURE Drs Kolker, Halyko, and Tigges have disclosed no financial relationships relevant to this article. Dr Halyko's current affiliation is Aurora Healthcare, Waterford, WI. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Human parechoviruses (HPeVs) are single-stranded, positive sense RNA viruses that belong to the large family of Picornaviridae. They were first discovered during a diarrheal outbreak in the United States more than 50 years ago and were initially described as echovirus 22 and 23 based on their similar clinical presentation and cytopathology with enteroviruses. Recently, the viruses have been reclassified into their own genus, with 16 currently recognized types labeled HPeV1 to HPeV16. HPeV1 and HPeV2 are the formerly named echoviruses 22 and 23, which represent the most prevalent forms of parechovirus.

Parechoviruses have been known to be a cause of infection in children, and most of these infections occur within the first year after birth. Seropositivity for parechovirus antibody to HPeV1 increased from 22% at 2 months of age to 88% at 2 years, confirming the very high incidence of HPeV1 infection in early childhood. (1) Similar results have been seen with HPeV3.

HPeV1 is the most prevalent parechovirus and generally causes gastrointestinal or respiratory illness. HPeV1 has also been found in sporadic cases of aseptic meningitis, with these infections being more prevalent in the late summer and early winter months. (2)(3)

Recently, HPeV3 has emerged as a common cause of meningitis and neonatal sepsis. The presentation of HPeV3 infection is similar to that of enterovirus, with fever, seizure, irritability, rash, and feeding problems. In a Scottish study, HPeV was reported in 14 of 1,575 CSF samples. All of these patients were younger than 3 months, and further studies determined that HPeV3 was the source for all these infections. (1) This study, as well as others, suggests that HPeV3 has a propensity for causing central nervous system (CNS) infection. Other investigators have used real-time PCR to study the replication of HPeV1 and HPeV3 in gastrointestinal, respiratory, and neuronal cell lines. They found no significant difference in the rate of replication of HPeV1 in various cells but found that HPeV3 strains replicated more rapidly in neuronal cells. (1)(4)

Although HPeV3 has been associated with relatively benign cases of meningitis and neonatal sepsis, it also has been shown to cause more severe CNS infection, including encephalitis. The Australian Childhood Encephalitis Study identified 13 cases of suspected HPeV encephalitis. They did not type these HPeV infections, although they hypothesized that HPeV3 was the cause because of its relative prevalence. In this study, 9 of the 13 patients had confirmed encephalitis as deemed by an expert panel, and the other 4 patients were classified as not having encephalitis but had positive CSF PCR for HPeV. The study found that there were significant neurodevelopmental concerns at 12 months in 7 of 8 children in the encephalitis cohort. There were no neurodevelopmental concerns in the 4 patients in the nonencephalitis cohort. (5)

To date, HPeV meningitis has been hypothesized to have similar neurodevelopmental outcomes to that of enterovirus meningitis. Many long-term studies have been performed to assess the outcomes of enteroviral meningitis and have demonstrated no significant long-term neurodevelopmental abnormalities for children with mild CNS involvement. For children with more severe CNS involvement, including encephalitis and/or CNS involvement leading to cardiopulmonary failure, neurodevelopmental outcomes have not been as good. (2) Long-term studies have not yet been performed in populations with HPeV meningitis.

Although it may be intuitive, several studies have suggested older siblings as a primary source of infection. A Dutch study found that second-born children had a 9-fold increased risk of developing HPeV3 infection and an 11-fold increased risk if siblings were less than 2 years apart in age. (6) Finally, a Japanese study of 43 neonates and young infants with HPeV3 found that the infants infected with HPeV3 were more likely to have siblings than the general population. These findings suggest that older siblings are a likely source for HPeV infection in neonates, and the presence of an older sibling may increase the index of suspicion for parechovirus infection. (7)

The true incidence and prevalence of HPeV meningitis and encephalitis are likely underreported due to lack of routine testing. As mentioned previously herein, at the time of presentation our institution did not have an available approved test for HPeV. Lack of testing for HPeV has important clinical consequences. Access to PCR for HPeV could lead to decreased use of antibiotic agents and longer length of stay in patients found to be HPeV positive, similar to patients found to be enterovirus positive. These consequences support the need for a fast and reliable test for HPeV.

A newly approved PCR test that can detect 14 pathogens including HPeV holds promise for increasing the ability to diagnose HPeV meningitis and encephalitis. In a multicenter evaluation, the sensitivity and specificity for HPeV were 100% and 99.8%, respectively. (8) HPeV testing could potentially allow for the more prudent use of antibiotic drugs, decreased length of hospital stay, and better informed counseling of patients' families.

Although infection with HPeV is common, no antiviral medications are currently approved. (2) An oral viral

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capsid inhibitor, pleconaril, has been shown to have activity against viruses from the Picornaviridae family. Abzug et al performed a randomized controlled trial and reported a shorter time to PCR and culture negativity, as well as greater survival, in neonates with enteroviral sepsis who received pleconaril. (9) Other additional studies have suggested benefit for pleconaril recipients and have demonstrated that pleconaril is generally well-tolerated, but clinical outcome in treated patients varied considerably. Administration of intravenous immunoglobulin is an additional treatment option, but the outcome was variable with this treatment as well. In summary, more studies are needed to evaluate the effectiveness of antiviral medications, and current treatment consists of supportive care.

Although he remained clinically stable, our patient was hospitalized on prophylactic ceftazidime until his absolute neutrophil count was greater than $500/\mu L$ ($0.50 \times 10^9/L$). He was subsequently discharged on hospital day 6 without sequelae.

Lessons for the Clinician

- Parechoviruses are a well-known but underrecognized source of infection and fever in infants.
- The use of new polymerase chain reaction testing allows for quick identification of parechoviral infections.
- Parechoviruses commonly cause gastrointestinal and/or respiratory illnesses but are also known to cause central nervous system (CNS) infections as well.
- Mild CNS infections are thought to be well tolerated, similar to enteroviral CNS infections, without significant neurodevelopmental deficits.
- More serious infections associated with encephalitis may result in neurodevelopmental deficits, but more research is needed to understand its true effects.
- Pediatric health-care providers should be aware of parechovirus as a potential cause of fever in neonates and be prepared to counsel families on its treatment, expected course, and long-term outcomes.

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4 Large-Volume Hematemesis in a 16-year-old Boy

Soham Dasgupta, MD,* Oluwabunmi O. Olaloye, MD,[†]
Matthew A. Pierce, MD,[‡] Andrea M. Glaser, MD[§]

*Department of Cardiology, Children's Healthcare of Atlanta, Atlanta, GA
[†]Department of Newborn Medicine, Magee-Womens Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA
[‡]Department of Emergency Medicine, Rady Children's Hospital, San Diego, CA
[§]Department of Gastroenterology, Hepatology, and Nutrition, University of Texas Medical Branch, Galveston, TX

PRESENTATION

A 16-year-old Hispanic boy presents to our emergency department (ED) with recurrent episodes of bloody emesis. Two other episodes occurred 1 and 3 months before the current presentation. The volume of bloody emesis during these episodes was small and without associated hemodynamic instability. However, the family did not have any health insurance secondary to absence of a legal immigration status, declined further evaluation, and missed their follow-up appointments. In the ED, the patient is tachycardic and diaphoretic with a supine heart rate of 140 beats/min and blood pressure of 78/50 mm Hg, a respiratory rate of 25 breaths/min, and oxygen saturation of 95% on room air. He experiences a brief syncopal episode on sitting upright and is subsequently administered 2 normal saline boluses (1 L each). His initial hemoglobin level is noted to be 8 g/dL (80 g/L), and transfusion of 1 U of packed red blood cells is initiated. Initial laboratory values are noted as follows: serum sodium, 137 mEq/L (137 mmol/L); potassium, 4.2 mEq/L (4.2 mmol/L), chloride, 102 mEq/L (102 mmol/L), bicarbonate, 24 mEq/L (24 mmol/L), blood urea nitrogen, 26 mg/dL (9.3 mmol/L), creatinine, 0.68 mg/dL (51.9 μmol/L), albumin, 3.5 g/dL (35 g/L), aspartate aminotransferase, 30 U/L (0.50 μkat/L), alanine aminotransferase, 37 U/L (0.62 μkat/L), total bilirubin, 0.5 mg/dL (8.6 μmol/L), ammonia, 38 μg/dL (27.1 μmol/L), prothrombin time, 16.7 seconds, and activated partial thromboplastin time, 25 seconds. A nasogastric tube is inserted, and cold-water lavage is instilled, which causes the patient to have a large-volume bloody emesis. On arrival at the PICU, he is started on pantoprazole and octreotide drips, and the pediatric surgery and gastroenterology services are consulted.

His bleeding is not controlled while receiving pantoprazole and octreotide drips for an hour. Owing to hypovolemic hemorrhagic shock, he is electively intubated, and emergency bedside esophagogastroduodenoscopy (EGD) is performed. EGD reveals extensive gastroesophageal varices with a positive nipple sign suggestive of recent bleeding (Figs 1 and 2). A total of 6 esophageal varices are banded, and bleeding is temporarily stopped. Within 30 minutes of banding, the

AUTHOR DISCLOSURE Drs Dasgupta, Olaloye, Pierce, and Glaser have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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patient has another large-volume bloody emesis. EGD is again performed and reveals active bleeding from an unbanded varix at the gastroesophageal junction. His hypovolemic hemorrhagic shock subsequently worsens, requiring initiation of an institutionally based massive transfusion protocol. He receives 8 U of packed red blood cells, 6 U of fresh frozen plasma, 6 U of platelets, 4 U of cryoprecipitate, and 1 mg of factor VII. Upper gastrointestinal bleeding is eventually controlled with placement of a Sengstaken-Blakemore tube under tension with balloon inflation, allowing for tamponade of gastric and esophageal varices. Abdominal ultrasonography demonstrates absent flow in the portal vein, and additional computed tomography (CT) reveals the diagnosis.

DISCUSSION

A CT scan of the abdomen demonstrated cavernous transformation of the portal vein, prominent gastroesophageal varices, and splenomegaly measuring 17.1 cm (Fig 3). Radiographic and clinical findings were suggestive of chronic occlusion of the portal vein. There is no known family history of clotting disorders, and he did not have any stigmata of chronic liver disease or ascites on physical examination; also, he never had an umbilical line placed. On day 5 of hospitalization, surgical repair with a meso-Rex bypass procedure is attempted. However, due to the small caliber of intrahepatic portal vein branches, a distal splenorenal shunt is successfully performed instead. Subsequent CT shows a decrease in size of the gastroesophageal varices. Evaluation for hypercoagulability disorders reveals elevated levels of immunoglobulin (Ig) M, IgG, and IgA anti-$\beta 2$ glycoprotein I antibody (26.7, 56.8, and 45.8 SU, respectively; reference range, 0–20 SU), suggestive of antiphospholipid antibody syndrome (APS). He is discharged on hospital day 14 with low-dose aspirin and close outpatient follow-up. A liver biopsy is pending at the time of discharge.

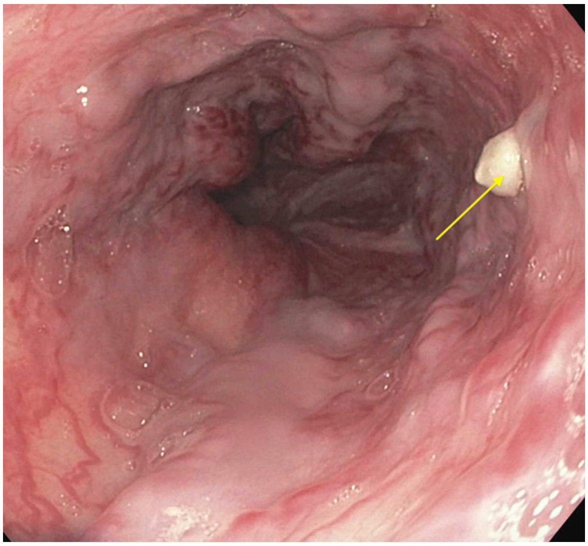

Figure 1. Esophagogastroduodenoscopy demonstrating large esophageal varices with a positive nipple sign (arrow) suggestive of recent bleeding.

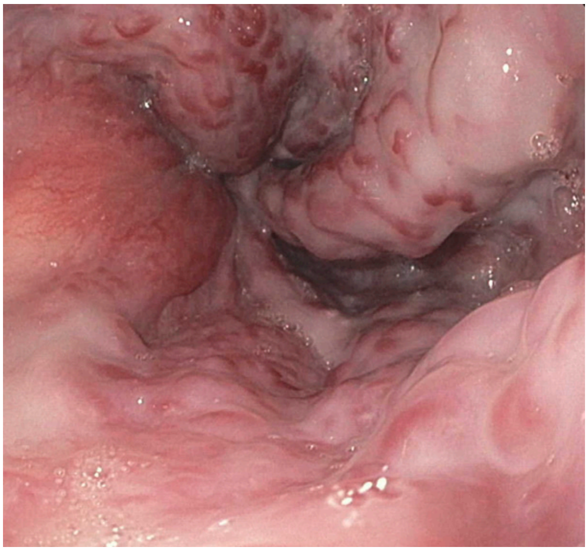

Figure 2. Esophagogastroduodenoscopy demonstrating large esophageal varices.

THE CONDITION

Upper gastrointestinal bleeding may manifest as hematemesis, melena, or, rarely, hematochezia and has a broad

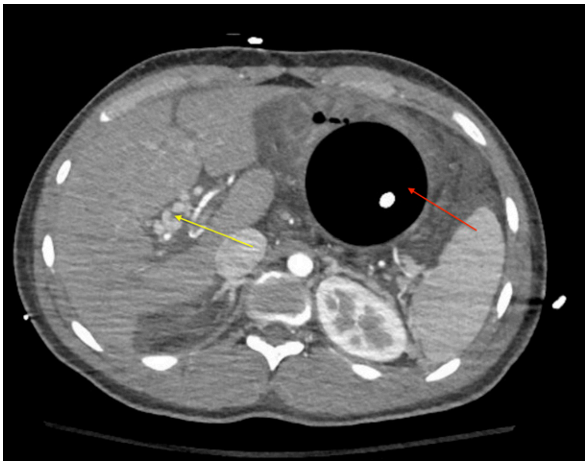

Figure 3. Computed tomographic scan of the abdomen demonstrating cavernous transformation of the portal vein with collateral formation (yellow arrow) and the presence of a Sengstaken-Blakemore tube (red arrow).

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TABLE. Common Conditions Leading to Extrahepatic Portal Vein Obstruction and Their Pathophysiologic Mechanisms

PATHOPHYSIOLOGIC MECHANISM	CONDITION
Portal flow obstruction	Cirrhosis Tumor obstructing portal vein Budd-Chiari syndrome
Hypercoagulable states	Inherited thrombophilia Factor V Leiden Prothrombin gene mutation Protein C and S deficiency Antithrombin III deficiency *MTHFR* gene mutation Acquired thrombophilia Myeloproliferative disorder Antiphospholipid syndrome Hyperhomocysteinemia Paroxysmal nocturnal hemoglobinuria Pregnancy/puerperium Oral contraceptives Sepsis Cirrhosis
Vascular damage	Trauma Surgery Liver transplant Invasive procedures Infections
Malignancy	Hepatocellular carcinoma Cholangiocarcinoma

differential diagnosis. (1) The causes of upper gastrointestinal bleeding vary by age. The most common cause in the neonatal age group is swallowed maternal blood followed by gastritis, and peptic ulcer is the most common cause in patients aged 3 to 5 years. (2) Mallory-Weiss tear is also a frequent cause in this age group and in older children. It is due to a mucosal laceration at the gastroesophageal junction usually secondary to excessive retching and vomiting. (3) In

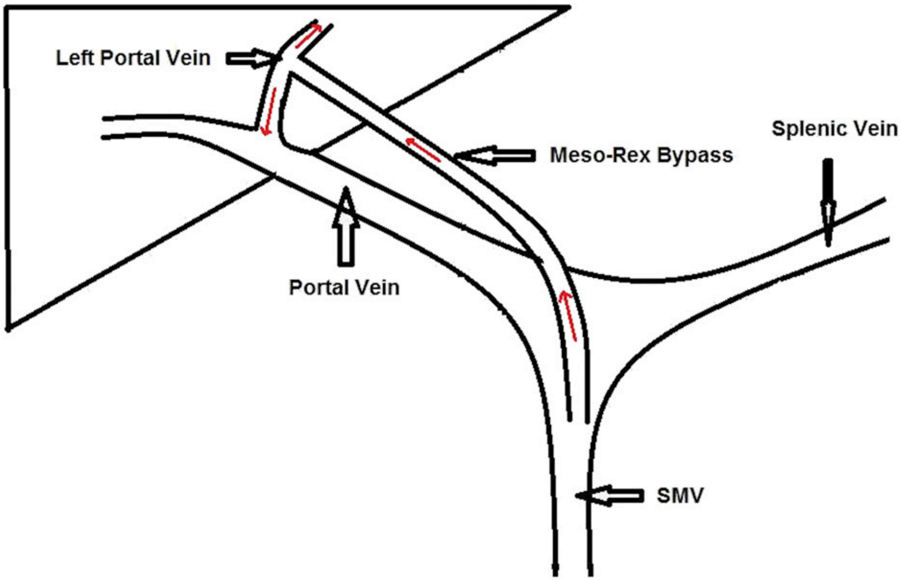

Figure 4. Meso-Rex bypass: graft bypassing the occlusion in the portal vein via conduit from the left portal vein to the superior mesenteric vein (SMV) with blood flow to the right portal vein.

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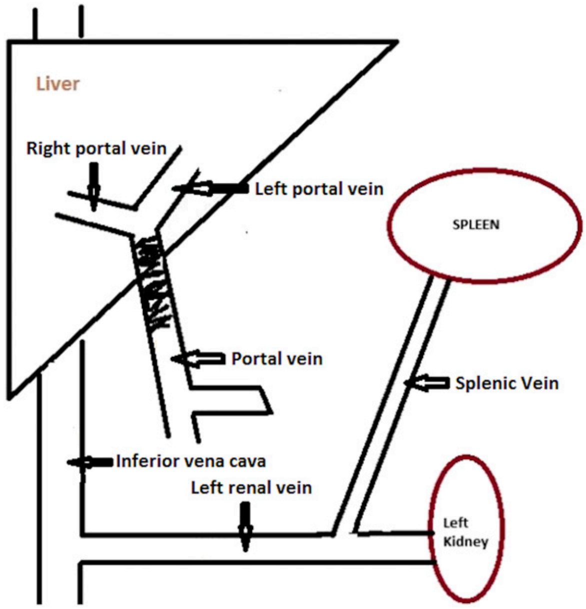

Figure 5. Distal splenorenal shunt: the splenic vein is surgically connected to the left renal vein.

children older than 5 years, esophageal varices secondary to portal hypertension is the most common cause and may present with life-threatening hematemesis. (2) The causes of portal hypertension are multiple, 1 of which is extrahepatic portal vein obstruction (EHPVO).

EHPVO is defined as obstruction of the extrahepatic portion of the portal vein that may or may not involve the intrahepatic portal veins. (4) It, however, does not refer to isolated thrombosis of the splenic or superior mesenteric vein. (4) EHPVO is responsible for 5% to 10% of all cases of portal hypertension in developed countries and is most commonly secondary to underlying liver disease or malignancy (Table). (5)(6)

The portal vein is formed by the splenic vein and the superior and inferior mesenteric veins. It supplies 75% of the blood to the liver, and the remaining 25% is supplied by the hepatic artery. (7) In chronic EHPVO, the normal single-channel portal vein becomes bypassed by numerous tortuous collateral venous channels forming a portal cavernoma. It takes 3 to 5 weeks for these collateral venous channels to become fully established. (8)

Acute EHPVO may manifest with symptoms of abdominal pain and ascites but is often asymptomatic. As the portal cavernoma becomes unable to accommodate splenomesenteric inflow, signs of portal hypertension develop. (6)(9) Acute variceal bleeding is the most frequent and may be the first manifestation of a failing portal cavernoma. (9) The

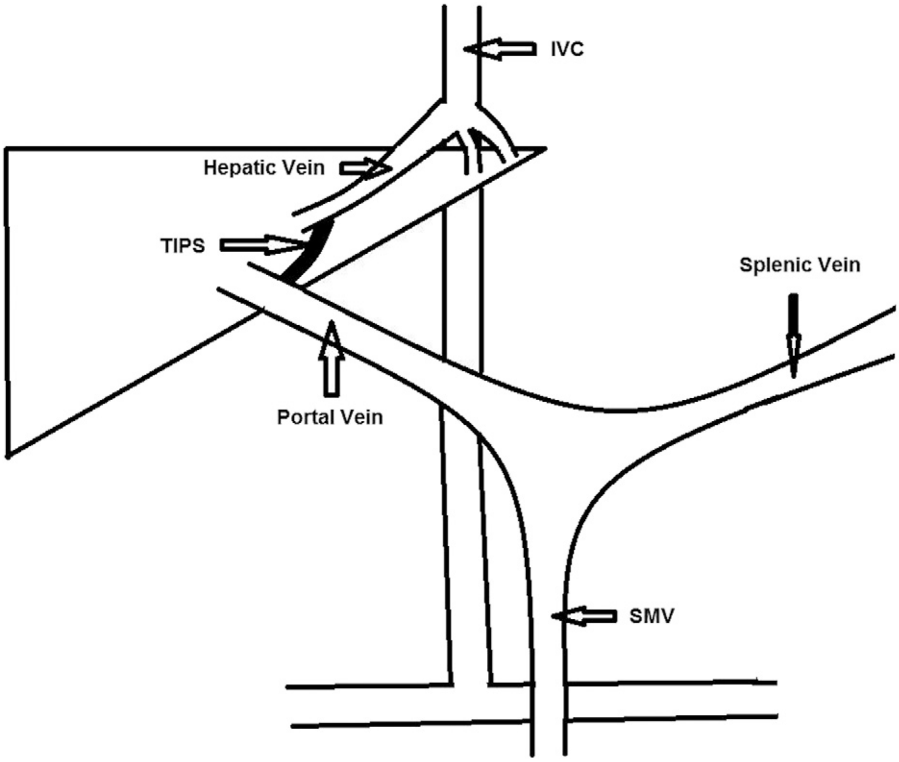

Figure 6. Transjugular intrahepatic portosystemic shunt (TIPS): the portal vein is connected to the hepatic vein. IVC=inferior vena cava, SMV=superior mesenteric vein.

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gastroesophageal varices are usually large, and gastric varices are seen in 30% to 40% of patients. (10) Interestingly, ascites is a rare complication of chronic portal vein obstruction.

Our patient presented in hypovolemic hemorrhagic shock due to acute variceal bleeding. EGD demonstrated large gastric and esophageal varices, and CT confirmed the diagnosis of chronic EHPVO. Evaluation for a hypercoagulable condition revealed elevated anti-$\beta 2$ glycoprotein I antibodies, suggestive of APS. APS is an acquired autoimmune disorder that manifests as recurrent venous or arterial thrombi. (11) Diagnosis depends on characteristic clinical features and laboratory abnormalities on 2 or more samples collected at least 12 weeks apart.

DIAGNOSIS

Abdominal ultrasonography is a reliable, noninvasive technique to diagnose portal vein thrombosis and is the initial investigation of choice. (5) The overall sensitivity and specificity of Doppler ultrasonography in the diagnosis of portal vein thrombosis are reported to be 89% and 92%, respectively. (12) CT and magnetic resonance imaging provide additional information, such as thrombus extension (mesenteric veins are difficult to assess with ultrasonography), evidence of bowel infarction, and adjacent organ status. (13) EGD is necessary to demonstrate as well as manage bleeding esophageal/gastric varices, and a liver biopsy is necessary to rule out chronic liver disease, especially in a patient with abnormal liver function tests.

MANAGEMENT

The initial management of variceal bleeding is adequate resuscitation with fluid and blood products along with initiation of an intravenous proton pump inhibitor and octreotide drip. EGD is essential to demonstrate and manage the varices endoscopically. The most common endoscopic procedure used to control variceal bleeding is banding of the varices. Sometimes, placement of a Sengstaken-Blakemore tube may be a last-ditch effort to tamponade bleeding if banding fails. Surgical methods are used to control variceal bleeding in children with EHPVO when it is unresponsive to medical/endoscopic therapy. These therapies may include a portosystemic shunt or the Rex bypass procedure. (14) The Rex bypass is a procedure in which portal flow is redirected into the liver and, therefore, is not a shunt procedure (Fig 4). (15) This is done by bringing mesenteric venous and splenic blood around the EHPVO into a patent intrahepatic portal venous system, most commonly the left portal vein. However, the Rex bypass is suitable only for patients with a patent intrahepatic portal vein branch, determined by portal venography in the operating room. The distal splenorenal shunt is the procedure of choice for those who are not candidates for the Rex procedure (Fig 5). Transjugular intrahepatic portosystemic shunt is feasible only in patients with a patent portal vein lumen (Fig 6).

Lessons for the Clinician

- Maintain a high index of suspicion for isolated esophageal/gastric varices in an adolescent with large-volume hematemesis even in the absence of other stigmata of portal hypertension (ascites, caput medusae, hemorrhoids).
- Although local epidemiology leads us to believe that *Helicobacter pylori* is a common cause of upper gastrointestinal bleeding in the pediatric population (incidence 3%–10% in developing countries and 0.5% in developed countries), variceal bleeding must remain high on the differential diagnosis and is the most common cause in children older than 5 years.
- Mallory-Weiss tear is a common cause of upper gastrointestinal bleed.
- Surgery is essential for patients who fail medical and endoscopic therapy.

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Soham Dasgupta, Oluwabunmi O. Olaloye, Matthew A. Pierce and Andrea M. Glaser

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Salmonella Infections

Crystal R. Worsena, DO, MS,* Aaron S. Miller, MD, MSPH,* Marta A. King, MD, MEd*
*Department of Pediatrics, SSM Cardinal Glennon Children's Hospital, St Louis, MO

Salmonella, part of the Enterobacteriaceae family, are gram-negative, nonencapsulated, flagellated, facultative anaerobic, nonlactose fermenting bacilli that infect small intestinal epithelial cells. Pediatricians need to be familiar with the clinical features, epidemiology, diagnosis, management, and prevention of 3 distinct salmonellosis syndromes: nontyphoidal *Salmonella* (NTS) gastroenteritis, NTS extraintestinal disease, and typhoidal *Salmonella* (TS) enteric fever.

NTS infections are a worldwide common cause of gastrointestinal disease in immunocompetent individuals, whereas extraintestinal disease from NTS occurs predominantly in infants and other high-risk populations. TS are the cause of enteric (typhoid and paratyphoid) fever, a systemic disease with significant mortality and morbidity in developing countries.

NTS are a common cause of bacterial gastroenteritis worldwide, with 153 million cases leading to 57,000 deaths reported annually. In the United States, NTS cause 1.2 million illnesses and 450 deaths annually, with the highest incidence in children younger than 5 years. Most human NTS infections come from 2 serotypes of *Salmonella enterica:* Enteritidis and Typhimurium. NTS have a wide range of reservoirs and hosts, including humans, poultry, reptiles (turtles, lizards, snakes, iguanas), and amphibians (frogs, salamanders, newts). The major mode of transmission is by ingestion of contaminated animal food products. Other modes of transmission are contact with colonized animals, consumption of contaminated water and nonanimal food products, and fecal-oral spread. The most common sources of infection in the United States are chickens and eggs. Incubation is typically 6 to 12 hours (range, 6–72 hours). Immunocompetent individuals typically experience self-limited acute gastroenteritis with nausea, emesis, abdominal pain, fever, and watery, nonbloody diarrhea lasting less than 10 days. Some infected individuals can experience bloody diarrhea, whereas some may be asymptomatic. Extraintestinal disease, including bacteremia, meningitis, osteomyelitis, septic arthritis, pneumonia, and cholangitis, can occur, especially in high-risk populations and those infected with more virulent NTS serotypes. Individuals at higher risk for extraintestinal disease include infants, the elderly, those with compromised immune systems, and those with decreased stomach acidity. Patients with sickle cell disease are at increased risk for *Salmonella* osteomyelitis due to impaired splenic function and areas of bone infarction. Bacterial fecal shedding can continue for up to 3 monthes 12 weeks, especially in children younger than 5 years and in those treated with antibiotic drugs.

Enteric fever caused by TS is a severe illness with significant rates of morbidity and mortality in many parts of the developing world, with an estimated 31 million cases leading to more than 215,000 deaths worldwide annually. In the United States, enteric fever is rare, with approximately 400 cases annually, and is typically associated with international travel. TS species known to cause enteric fever are *Salmonella enterica* serotypes Typhi and Paratyphi, both with exclusive human

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reservoirs and fecal-oral transmission. The average incubation period is 7 to 14 days (range, 3–60 days). Symptoms include fever, chills, malaise, myalgias, headache, cough, jaundice, constipation, or diarrhea and typically last 2 to 4 weeks without treatment. The classic description of blanching, erythematous ("rose-colored") lesions on the trunk can be seen in the second week of illness, although this clinical finding is uncommon. Complications can include intestinal perforation, splenic and brain abscesses, disseminated intravascular coagulation, rhabdomyolysis with acute renal failure, and Guillain-Barre syndrome. Stool bacterial shedding continues for more than 3 months in approximately 10% and for more than a year in 4% of infected individuals. Individuals with prolonged fecal shedding might serve as infection reservoirs.

The NTS and TS serotypes induce different inflammatory responses. NTS invasion of small intestinal epithelial cells induces a robust local inflammatory response, typically limiting infection to the gastrointestinal tract. TS infection, on the other hand, does not induce a significant inflammatory response, allowing for bacterial invasion into the mesenteric lymphatic system and transient primary bacteremia. Typically, patients with TS are initially asymptomatic, and blood cultures are negative during the incubation period, which lasts 7 to 10 days after infection. From the bloodstream, bacteria disseminate to organs with a reticuloendothelial system (liver, spleen, gallbladder, bone marrow), where they multiply in macrophages and are shed into the bloodstream, resulting in sustained secondary bacteremia and symptom onset.

Diagnosis of NTS gastroenteritis is typically made by stool culture, and cultures from other sites (blood, cerebrospinal fluid, synovial fluid) confirm extraintestinal infection. Blood culture is the primary means of diagnosing TS enteric fever, with repeated cultures often required due to low sensitivity. Stool cultures have low diagnostic yield in TS. Most patients with NTS gastroenteritis have a normal complete blood cell count. Those with extraintestinal NTS and TS can have leukocytosis, leukopenia, anemia, and transaminitis. The Widal test is a rapid, inexpensive TS antibody test of low sensitivity and specificity but is widely used in developing countries to get preliminary results before blood culture positivity. Although additional commercial assays are emerging, they are not yet widely available.

Treatment of immunocompetent individuals with NTS gastroenteritis is supportive. Antibiotic drugs are not recommended because they do not shorten the illness and may cause prolonged fecal bacterial shedding. Hospitalization, blood cultures, and antibiotic drug therapy are indicated for NTS gastroenteritis in infants younger than 3 months and should be considered in other individuals at high risk for extraintestinal disease. Hospitalization and antibiotics (typically third-generation cephalosporins [ceftriaxone or cefotaxime]) are indicated for all individuals with NTS extraintestinal disease and those with TS. Because increasing *Salmonella* antibiotic drug resistance is a global public health concern, local susceptibility patterns should be taken into account in starting empirical treatment and therapy adjusted once sensitivities are available. Typical antibiotic drug therapy duration is 5 to 7 days for isolated gastroenteritis, 2 weeks for isolated bacteremia, and 4 to 6 weeks for extraintestinal infections. Those with severe enteric fever who present with shock, obtundation, or coma may benefit from systemic corticosteroids. Chronic TS carriers should be treated with 4 weeks of an oral fluoroquinolone after initial treatment and might require a cholecystectomy because carriage is thought to result from gallbladder biofilm formation.

There are currently no vaccines for either NTS or paratyphoid enteric fever. Two vaccines are available for *Salmonella* Typhi enteric fever. Vivotif® (Crucell Switzerland Ltd, Bern) is an oral live-attenuated vaccine approved for immunocompetent individuals 6 years and older. The vaccine requires 4 doses administered every other day. Typhim Vi® (Sanofi Pasteur Inc, Swiftwater, PA) is an intramuscular purified capsular antigen vaccine approved for individuals 2 years and older and requires a single dose. Neither vaccine provides complete protection. In enteric fever endemic areas, vaccination is recommended for all school-aged children. In the United States, vaccination is indicated for people traveling to endemic areas, those exposed to typhoid fever carriers, and laboratory workers in frequent contact with *Salmonella* Typhi.

Primary methods for *Salmonella* prevention include handwashing, proper disposal of human waste, and water treatment. In addition, avoiding contact with high-risk animals and thoroughly cooking food can prevent NTS. Families should be counseled about the potential risk of *Salmonella* carriage in high-risk pets and advised to keep pets and cages away from the kitchen or food preparation area and to wash hands after handling pets. High-risk pets

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should be avoided in child care centers, households with children younger than 5 years (especially infants), and other individuals at high risk for extraintestinal NTS disease. Although outbreaks in child care centers are rare; children with NTS gastroenteritis should be kept home until asymptomatic for at least 24 hours. Children with TS must not return to school or child care until they have 3 negative stool cultures obtained more than 48 hours after discontinuation of antibiotic drug therapy. All cases of *Salmonella* infection must be reported to the health department.

Although NTS *Salmonella* typically causes self-limited gastroenteritis requiring only supportive care, pediatricians need to be aware of the possibility of extraintestinal infection, especially in high-risk populations. TS enteric fever is a serious systemic illness common in areas of the developing world. Both NTS extraintestinal illness and TS require hospitalization and intravenous antibiotic drug therapy. Prevention is primarily through appropriate hygiene and avoidance of contact with high-risk pets.

COMMENT: *Salmonella* infections are fascinating in that more than 2,600 serotypes have been identified. The wide range of clinical presentations, from asymptomatic carriage to serious invasive disease leading to morbidity and even death, depends on the interplay between the virulence of the serotypes and the host factors. As mentioned in the *In Brief,* it is critical to not use antibiotic drugs in low-risk patients with uncomplicated *Salmonella* NTS gastroenteritis because this disease is self-limited, antibiotic drug administration can prolong the carrier stage, and the indiscriminant use of antibiotic agents contributes to the development of resistant organisms. In contrast, TS infections require treatment with antibiotic drugs due to the significant morbidity and mortality that can result. Hence, familiarity with the various presentations and access to a laboratory with the sophisticated ability for correct serotype identification is critical. I remember 2 recent patients for whom I provided care. One was a young, malnourished boy from Nigeria who presented with fever without an obvious etiology and was determined to have typhoid fever by serial blood cultures. Hence, the importance of obtaining blood cultures in febrile children without an etiology, especially when foreign travel is known. The other patient was a 7-month-old with *Salmonella* gastroenteritis. Through some detective work and good questioning on the part of an astute house officer, it was determined that the parents had given the infant a chicken bone from dinner to chew on as a pacifier because she was teething. Determining the etiology of *Salmonella* infections is important to provide more education to families and the community.

Because positive *Salmonella* cultures should be reported to local health departments, this surveillance in collaboration with the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) is incredibly helpful in identifying outbreaks, high-risk practices, or contamination of food products to inform population health.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

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in Brief

Corticosteroids

Carolyn M. Rosen, MD*
Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY

Corticosteroids are one of the most important classes of anti-inflammatory and immune modulators in a physician's arsenal to help treat a variety of conditions. They also have significant adverse effects with short- and long-term use and, therefore, need to be prescribed judiciously. This article briefly reviews the uses and adverse effects of corticosteroids.

Corticosteroids have been used to treat a wide range of diseases, including allergic, dermatologic, gastrointestinal, and hematologic/oncologic disorders; some infectious diseases; organ transplant; renal disease; and respiratory and rheumatologic disorders. In some cases, such as acute asthma exacerbations, a short course of oral corticosteroids is used for 3 to 5 days. In other situations, patients need to take corticosteroids for much longer, sometimes months to years. In general, if someone has been receiving systemic corticosteroids for less than 10 to 14 days, it is deemed safe to vaccinate him or her, including with live viral vaccines, per the *Red Book*. However, it is recommended to try to limit the duration to the shortest time possible and the amount/dose of corticosteroids to the lowest potency to achieve the desired results.

ADVERSE EFFECTS WITH LONG-TERM USE

There are many adverse effects due to long-term use of corticosteroids, defined as continued use of oral or intravenous corticosteroids for more than 14 days. With several important exceptions, most of these effects are reversed or partly reversed with discontinuation of the corticosteroid medication. However, cataract formation, earlier development of atherosclerotic disease, and bone abnormalities (osteoporosis and osteonecrosis) are, in general, unchanged by stopping medication. The adverse effects of long-term corticosteroid use are many and include the aforementioned osteoporosis and cataract formation, in addition to hypothalamic-pituitary-adrenal (HPA) axis suppression, cushingoid appearance with weight gain, diabetes, cardiovascular disorders, elevation of cholesterol level, immunosuppression, behavioral changes (such as aggressive behavior, inattentiveness, mood swings, and sleep disturbances), gastrointestinal problems (gastritis and gastrointestinal bleeding), and skin manifestations (skin thinning, ecchymoses, acne, and striae). Finally, growth suppression is a problem that is unique to the pediatric population.

A variety of studies of children with chronic medical disorders have been published showing that children's final height is less than would have otherwise been expected when taking long-term systemic corticosteroids. One study looked at children with cystic fibrosis who were placed on either every-other-day prednisone treatment versus placebo. The children were followed for many years after stopping treatment, and boys, in particular, were found to be significantly shorter compared with those receiving placebo after 18 years of age.

AUTHOR DISCLOSURE Dr Rosen has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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A systematic review of studies that looked at adverse effects of long-term use of corticosteroids in children was recently published. The reasons for corticosteroid use varied and included leukemia, respiratory diseases such as asthma and cystic fibrosis, nephrotic syndrome, and Crohn's disease. According to this review, the most common complications seen with oral corticosteroid therapy were weight gain, growth suppression, and features of Cushing syndrome. In addition, when tested, more than half of the children showed HPA axis suppression. Several of these children did not regain appropriate adrenal function for up to 4 to 8 months after withdrawal of corticosteroids. The most common reason for stopping the corticosteroid medication was behavioral changes. In 1 particular study that looked at long-term use of corticosteroids in children diagnosed as having leukemia, patients who were older (>10 years) and were taking dexamethasone versus prednisone were more likely to be immunosuppressed.

The most serious complication noted in this systematic review was increased susceptibility to infection, which resulted in several deaths. Compared with the incidence of infection reported with short-course oral corticosteroids, the risk of infection was much greater with long-term use of corticosteroids (8.7% versus <1%). The most frequent culprit in deaths due to infection was found to be varicella.

ADVERSE EFFECTS WITH SHORT-TERM USE

Although there are widely known adverse effects to long-term use of corticosteroids, there are adverse effects to short courses of systemic corticosteroids as well. A recent systematic review of adverse effects of short courses of corticosteroids (<14 days) was published. The most serious adverse effect was infection due to immunosuppression, which occurred less than 1% of the time. The most common infection was again due to varicella. The more common adverse effects of short courses of corticosteroids included vomiting, behavior changes, and sleep disturbances, in order of decreasing frequency. Vomiting was associated with larger doses of corticosteroids and was noted, in particular, with use of oral prednisolone. The higher the dose, the more likely the patient would experience vomiting. This was the leading cause of patient nonadherence to corticosteroid treatment. A similar dose effect was seen with behavioral changes (anxiety, hyperactivity, and aggressive behavior), with these changes seen more frequently with higher doses of corticosteroids. In studies that documented blood pressure and weight, almost one-third of children experienced blood pressure elevation and weight gain, although these adverse effects were noted to be transient and resolved after discontinuation.

ADVERSE EFFECTS OF INHALED CORTICOSTEROIDS

Although inhaled corticosteroids, which are the mainstay of therapy for children with persistent asthma, are believed to have fewer adverse effects than systemic corticosteroids, adverse reactions still occur. Local adverse effects include oral candidiasis, cough, hoarse voice, and dysphonia. All of these are dose related and can be somewhat mitigated by using a spacer with a metered dose inhaler and rinsing the mouth immediately after use.

Systemic adverse effects of inhaled corticosteroids depend on the dose administered, how the medication is delivered (dry powdered inhaler, metered dose inhaler with and without spacer, nebulized medication), and the individual patient's response to corticosteroid therapy. HPA axis suppression has been found in children who are taking high dosages of inhaled corticosteroids as well as long-term use (>6 months' duration). In addition, growth suppression has been noted in children who used inhaled corticosteroids for longer than 12 months. Although some studies seemed to show that children using inhaled corticosteroids for varying periods ultimately obtained their normal adult height, a meta-analysis showed that the initial loss of height during the first year of inhaled corticosteroid use was never recovered. Bone density mineralization and fractures do not seem to be associated with low- to medium-dose inhaled corticosteroids; however, this can be complicated by the fact that children with persistent asthma also receive courses of systemic corticosteroids during acute exacerbations.

RECOMMENDATIONS FOR MONITORING

In general, patients receiving long-term systemic corticosteroids should be monitored at least every 6 months, and children younger than 2 years should be monitored every 3 months. A baseline assessment should include weight, height, blood pressure, complete blood cell count, glucose level, lipid levels, and consideration of a bone density test. In addition, pubertal status and growth should be closely monitored. Currently there are no established guidelines, to our knowledge, regarding when to assess a patient for HPA axis suppression. HPA axis suppression does occur

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when children have received systemic corticosteroids for more than 2 weeks. In addition, physicians should be aware that children who have received high-dose inhaled corticosteroids (equivalent to >500 μg/d of fluticasone) can also be at risk for HPA axis suppression if linear growth seems to be affected. Clinicians should use their judgment as to when to perform HPA axis testing. Questions regarding possible symptoms of diabetes should be asked, and patients should be referred for an annual ophthalmologic examination to check for cataracts or glaucoma. Patients and families need to be counseled to seek medical attention for any sign of infection. Stress dosing of corticosteroids needs to be considered to help prevent adrenal crisis. If the child has minor stress, such as a viral infection, low-grade fever, or minor surgery, the dose of corticosteroids should be doubled. For situations considered major stress, such as severe infection or major surgery, the child should be given hydrocortisone intravenously/intramuscularly 100 mg/m^2 followed by 25 mg/m^2 every 6 hours, and an endocrinologist should be consulted. The family must be educated about this possibility and should carry documentation of medications taken to prevent any possible oversight because this could lead to adrenal crisis. When the plan is to discontinue corticosteroids, tapering of corticosteroids should be initiated when children have been receiving long-term courses of corticosteroids.

In summary, corticosteroids are an extremely effective class of medications that play a role in the management of many chronic diseases. However, the adverse effects of corticosteroids can be quite serious. Every effort should be made to minimize the duration of treatment and the amount/dosage of corticosteroids needed. Close monitoring of potential adverse effects is imperative.

COMMENT: This *In Brief* really made me pause and think of all the patients I have cared for who have been prescribed corticosteroids with various doses and durations of treatment. As primary care health providers care for more children with chronic medical conditions, it is critical to know the benefits, adverse effects, and monitoring strategies of patients taking corticosteroids, as the author of this *In Brief* outlines so well. As with any medication, balancing the lowest-potency dose and shortest duration that still provides the desired medicinal benefits is critical to minimize morbidity. Although corticosteroids are important medications, their potential adverse effects are multiple and may vary by patient. The possible effect on bone health is significant for children in age groups and with chronic medical problems who are already at risk. Also, it is important to remember that corticosteroids have 2 properties: immunosuppression and anti-inflammatory responses that can affect a body's response to infections. Vigilance by parents, patients, and health-care providers for the possible development of infections is essential because the immunosuppression effect can lead to more virulent infections with common viruses, yet the anti-inflammatory properties can lead to a modification of symptoms and subsequent delay in diagnosis of these infections. The primary care provider has a critical role in both judicious prescribing and partnering with subspecialists to ensure that their shared patients with chronic medical problems are being monitored for adverse effects while also ensuring the shortest duration of exposure to corticosteroids as warranted by their symptoms and disease.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

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Corticosteroids

Carolyn M. Rosen

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Visual Diagnosis

The Blue Baby: An Infant Presenting with Severe Respiratory Distress

Jane Soung, MD,* Sriram Ramgopal, MD,* Brett McAninch, MD*

*Division of Pediatric Emergency Medicine, Department of Pediatrics, Children's Hospital of Pittsburgh, Pittsburgh, PA

PRESENTATION

An 8-month-old previously healthy girl presents to the emergency department with concerns of "not breathing right." Just before arrival she awoke from her nap screaming. She appeared grey and was breathing rapidly. Her babysitter called 911, and she was brought to the emergency department for further care. The patient had an isolated tactile temperature 4 days before arrival and has been having nasal congestion for approximately 1 week. There are no sick contacts in the household, and the child attends an in-home child care. Her medical history includes term vaginal delivery, up-to-date immunizations, and a maternal uncle with cystic fibrosis.

In the emergency department the child is cyanotic and is crying vigorously. Her pulse oximetry is 66% on room air, although there is difficulty getting a proper reading on the pulse oximeter. She is afebrile, her heart rate is 186 beats/min, blood pressure is 112/66 mm Hg, and respiratory rate is 58 breaths/min. There is bilateral air entry on the respiratory examination without audible wheeze or crackles. Cardiac examination is significant for tachycardia but with regular rhythm and without gallop or appreciable murmur. The remainder of the child's examination findings are normal. She is placed on a nonrebreather mask, her color improves, and pulse oximetry increases to the 80s. A venous blood gas shows pH 7.23, $P\text{co}_2$ of 51 mm Hg, and a bicarbonate level of 21 mEq/L (21 mmol/L).

Given this child's respiratory distress and decreased oxygen saturation, a portable anteroposterior chest radiograph is obtained (Fig 1).

Because of the child's continued hypoxia not improving on a nonrebreather, the decision is made to intubate. After administration of ketamine and rocuronium, the patient is intubated using a 4.0-mm cuffed endotracheal tube. Placement of the endotracheal tube is confirmed with end-tidal capnography, auscultation, and repeated chest radiograph. Given her initial chest radiograph, computed tomography (CT) of the chest is subsequently performed (Fig 2) and suggests the diagnosis.

DIAGNOSIS

The differential diagnoses for this baby's respiratory distress included respiratory infection (viral or bacterial), pneumothorax, congenital diaphragmatic hernia, mediastinal mass, and foreign body aspiration. Her chest radiograph was not consistent with a focal consolidation or tension pneumothorax. CT of the chest revealed an ovoid, well-circumscribed hyperattenuating lesion in the proximal

AUTHOR DISCLOSURE Drs Soung, Ramgopal, and McAninch have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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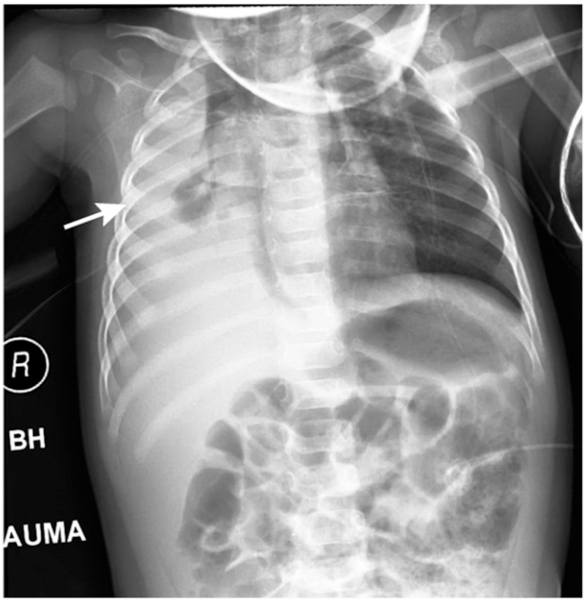

Figure 1. Initial anteroposterior radiograph showing almost complete opacification of the right hemithorax (arrow). Note no mediastinal shift and normal left lung markings without opacification.

right mainstem bronchus causing complete right lung collapse. The mass noted in the CT scan was most suggestive of a nonmetallic foreign body.

DISCUSSION

Etiology

Airway foreign bodies are a leading cause of morbidity and mortality in infants and toddlers. Both food and nonfood objects can cause airway obstruction. Foreign body ingestions remain in the top 5 causes of unintentional injury in children 4 years and younger in the United States. (1) Data from the Healthcare Cost and Utilization Project suggest that the mortality of airway foreign bodies is approximately 2.5%. (2) In 2014, airway foreign bodies in children accounted for more than 4,500 deaths in children. (1)

Most airway foreign bodies occur in younger children. A single-center 10-year retrospective study identified that children younger than 3 years accounted for three-quarters of all airway foreign bodies requiring surgical removal. (3) Data derived from the National Electronic Injury Surveillance System suggest that children younger than 1 year may be at particularly high risk. (4) A 2:1 male predominance has also been noted, which may relate to increased risk-taking behavior in young boys. (3)(5) Younger children are at risk because they have the greatest tendency to explore and place objects in their mouths while they are still developing their ability to swallow. Younger children may also chew their food poorly compared with older children due to a lack of posterior molars and distractions while eating. This, combined with their small airway diameter, places young children at the greatest risk for airway obstruction. Even nonmobile infants are at risk for aspiration if given food or small objects by older siblings.

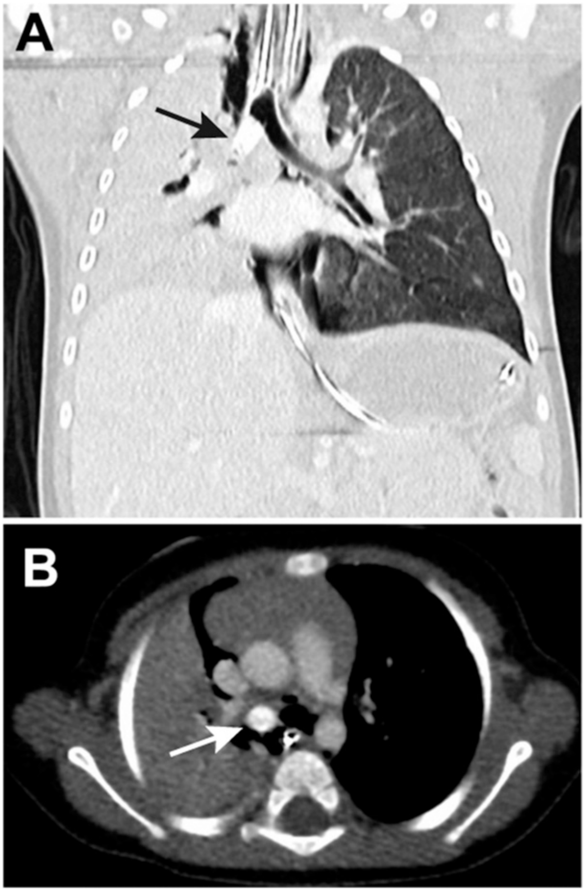

Figure 2. Sagittal (A) and axial (B) computed tomographic scans obtained after placement of an endotracheal tube. An ovoid, well-circumscribed, hyperattenuating lesion (arrows) is located in the proximal right mainstem bronchus, causing complete right lung collapse.

Common ingested objects include food, coins, toys, or small toy parts. In a meta-analysis published in 2012, organic foreign bodies constituted 76% of airway foreign bodies. Of these, nuts accounted for approximately one-third of aspirated objects. (6) Other concerning food items include hot dogs, seeds, popcorn, dried beans, hard candy, grapes, and pieces of carrot or apple.

Presentation: Signs and Symptoms

The classic triad of choking, wheezing, and unilaterally reduced breath sounds occurs in a minority of patients and should not be relied on to establish the diagnosis. (3) Because the presentation can be acute or subacute, the diagnosis can be missed. Coughing, choking, or gagging

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immediately after the episode occurs frequently. However, it may not be recognized by parents, and such history may not be volunteered. (3)(5) There is often an interval where acute symptoms have resolved and the child is well-appearing with normal examination findings. A delay in diagnosis for several days is common, and a few children may have a completely normal examination. (5) Immediate or late complications of foreign body ingestions include obstruction, infection, or local erosion. Complete or near-complete obstruction of the airway resulting in respiratory distress is the most serious complication of foreign body aspiration.

Foreign bodies can become lodged in the airway or the esophagus. Airway foreign bodies are lodged in the right bronchus in approximately 60% of patients. (7) Laryngeal foreign bodies account for approximately 10% of cases, (8) and bilateral airway involvement is rare. (7) Sometimes, foreign bodies in the esophagus will compress the trachea and be mistaken for airway foreign bodies.

Diagnosis and Evaluation

An evaluation should be initiated in the presence of a concerning history, even if the child is well-appearing. Two-view radiographs with anteroposterior chest and lateral neck/chest views remain the initial test of choice. Because most foreign bodies are radiolucent, radiographic diagnosis relies on indirect evidence of the presence of a foreign body. A single-center study from Turkey identified a normal radiograph in nearly 50% of patients. A radiopaque foreign body was noted in one-quarter of patients. In the remainder, imaging findings included atelectasis, air trapping, consolidation, bronchiectasis, pneumonia, pneumothorax, mediastinal shift, and pneumomediastinum. (9) A clinical or radiographic suspicion of tension pneumothorax, which typically does not occur in the setting of airway foreign body, should prompt emergency needle decompression or thoracotomy. (6)

Bilateral decubitus radiographs are frequently obtained in the diagnosis of foreign body aspiration in younger children. In a healthy patient, the dependent lung will partially collapse. In a child with a foreign body, air trapping secondary to a foreign body may prevent this change. Although frequently used in many centers, such use of bilateral decubitus radiographs may increase the false-positive rate without increasing the rate of true-positives, as determined by a single-center retrospective series. In contrast, the addition of expiratory radiographs in children who are able to cooperate may improve the rate of true-positive studies. (8)

Treatment and Management

Bronchoscopy is the definitive diagnostic and management tool for airway foreign bodies. Even if imaging studies are negative, bronchoscopy should be performed if there is high suspicion for aspiration. Rigid bronchoscopy is used in most centers. Approximately 20% of patients who present with foreign body aspiration will require mechanical ventilation. (2)

Prevention of Foreign Bodies

Prevention of choking relies on awareness and careful supervision by parents, teachers, and other caregivers. The American Academy of Pediatrics does not recommend initiation of solid foods before age 4 months. Finger foods should not be started until children can sit up without support and can bring their hands or other objects to their mouth; these milestones are typically reached between 6 and 9 months of age. Foods should be soft, easy to swallow, and cut into small pieces. Foods that require chewing, such as hot dogs, cheeses, and whole peanuts, should be specifically avoided at this stage. (10) To add to the confusion, most foods marketed as ideal finger foods often do not meet the American Academy of Pediatrics requirements. (11)

Regarding inorganic choking hazards, the Federal Hazardous Substance Act of 1960 was amended in 1994 by the Child Safety Protection Act. These amended laws required better labeling of packages for small toys and other articles at high risk for choking and also bans any toy intended for use in children younger than 3 years that may have a risk of choking or aspiration. (12)

Patient Course

Otorhinolaryngology was consulted, and the child was taken to the operating room for direct laryngoscopy with bronchoscopy. During the procedure, friable food particles were noted completely occluding the right mainstem bronchus. The foreign body and mucus were removed from the bronchus and the child was transferred to the PICU. She was extubated to room air the following day and was subsequently discharged home in stable condition.

Summary

- Although the classic triad of foreign body aspiration includes choking, asymmetrical breath sounds, and wheezing, this is not seen in all patients.
- Two-view radiographs including anteroposterior chest and lateral neck/chest views are the best first-line test. However, radiographs can be normal in 30% to 50% of airway foreign bodies.
- Bronchoscopy is the definitive treatment for airway foreign bodies and should be performed if index of suspicion is high, even if imaging is negative.

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Jane Soung, Sriram Ramgopal and Brett McAninch

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Asthma

Shilpa J. Patel, MD, MPH,* Stephen J. Teach, MD, MPH*

*Division of Emergency Medicine, Children's National Medical Center, Washington, DC

Practice Gap

Asthma is the most common chronic respiratory disease of childhood, a leading cause of emergency department visits, and 1 of the top 3 indications for hospitalization in children. Despite advances in the management of pediatric asthma, significant disparities in care and outcomes persist. To bridge these gaps, we must embrace the concept of asthma care across the continuum and extend our reach beyond the immediate patient-provider visit.

Objectives

After completing this article, readers should be able to:

1. Understand trends in prevalence, outcomes, and health disparities in pediatric asthma.
2. Describe advances in understanding the pathophysiology of asthma.
3. Translate an understanding of asthma to a differential diagnosis in a child with wheeze.
4. Practice guideline-based management with accurate assessment of asthma severity and control.
5. Apply recent evidence-based emerging trends in the treatment of asthma.
6. Identify community-based strategies and quality improvement projects in your practice setting to ensure asthma care across the continuum for vulnerable children.

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ABBREVIATIONS

ARR	at-risk rate
CDC	Centers for Disease Control and Prevention
ED	emergency department
EILO	exercise-induced laryngeal obstruction
FeNO	fractional excretion of nitric oxide
FEV_1	forced expiratory volume in 1 second
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IL	interleukin
LAIV	live attenuated influenza vaccine
LTRA	leukotriene receptor antagonist
NAEPP	National Asthma Education and Prevention Program
PBR	population-based rate
PEF	peak expiratory flow
PFT	pulmonary function testing
SABA	short-acting inhaled β_2-agonist

INTRODUCTION

Asthma is defined by episodic and reversible airway constriction and inflammation in response to infection, environmental allergens, and irritants. It is a complex, multifactorial, and immune-mediated process that presents with various clinical phenotypes.

Despite novel treatments and guideline-based care, asthma remains a significant public health problem. Medical care, missed school, and missed work related to asthma continue to burden our communities, costing more than $80 billion each year. (1) Furthermore, asthma disproportionately affects minorities and socioeconomically disadvantaged children. (2) Black children have the

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highest asthma morbidity and mortality rates of any US group, with twice the emergency department (ED) visit/hospitalization rate and 9 times the mortality rate as white children. (3)(4)(5)

In 2012, the President's Task Force on Environmental Health Risks and Safety Risks to Children commissioned a cabinet-level, multiagency group to address overall asthma morbidity and its racial and ethnic disparities. (6) The group chose 4 integrated strategies.

- Remove barriers to guideline-based care.
- Improve the identification of at-risk children.
- Build capacity for integrated, community-based care.
- Support efforts to prevent asthma.

EPIDEMIOLOGY AND PREVALENCE

Asthma affects 1 in 12 US children aged 0 through 17 years. (3) After decades of increases, the prevalence of asthma in this group plateaued between 2010 and 2012, (2) decreased in 2013 from 9.3% in 2012 to 8.3%, and remained stable through 2016. (2)(3) In contrast, pediatric asthma prevalence in black children increased between 2001 and 2009, leveling off by 2013. (2) In 2016, asthma prevalence in black children rose sharply to 15.7% (a 2.3% increase from 2014 and 2015), twice that of white children. (3) This rate surpassed that of Puerto Rican children, who previously had the highest prevalence of asthma of all US children. (3) The prevalence of asthma in children in poverty did not decrease between 2001 and 2013 and remained high in 2016 (10.5%). (2)(3)

Outcomes

Asthma exacerbation is a leading cause of (ED) visits (7) and 1 of the top 3 indications for hospitalization in children. (8) Comparing asthma outcomes between subgroups, an at-risk rate (ARR) is preferred over the traditional population-based rate (PBR). (9) An ARR is the number of children with the outcome (eg, asthma hospitalization or death) divided by the total number of children at risk for that outcome (those with asthma). Conversely, a PBR is the number of children with the asthma outcome divided by the total population. PBRs measure the overall burden of disease in a particular population or subgroup, whereas an ARR accounts for differences in prevalence between subgroups to describe disparities.(4) Between 2001 and 2010, ARRs for black and white children revealed a decrease in racial disparities for ED visit and hospitalization rates and no change in death rate due to asthma. (4) It is important to note, however, that ARRs do not account for differences in underlying asthma severity. A 2013 analysis of hospitalizations for chronic conditions in the Pediatric Health Information System database found that black children had the highest asthma readmission rate (21.4%) of any race or ethnicity. (10) Finally, because ARRs rely on prevalence estimates, any undercounting of "current asthma" in disadvantaged groups could result in an overestimation of risk.

Disparities in asthma outcomes and prevalence also exist based on geographic location. (11)(12) In Washington, DC, for example, 1 in 9 children, compared with 1 in 12 nationally, had asthma in 2014. (13) In addition, children in DC with the highest rates of ED visits and hospitalizations for asthma live in socioeconomically disadvantaged neighborhoods. Geographic variation in DC is likely due to a variety of factors, including but not limited to race and socioeconomic status. Population health using geospatial mapping, (2) disease-specific registries based on local electronic health records, and higher-level data analytics (machine learning, artificial intelligence, etc) (14) are promising tools to identify and decrease disparities in asthma outcomes. Collaborative efforts should target hot spots to address the causes of disparate outcomes. (15) Examples include the following:

- Map local asthma prevalence using geographic information systems software to identify hot spots of poor asthma control (ED visits, hospitalizations, readmissions, ICU admission, or death). Investigate neighborhood-specific factors (access to routine primary care, [16] housing conditions) through focus groups or needs assessments and initiate quality improvement projects to improve asthma control.
- Create an asthma registry using data from a health system's electronic health records to identify an at-risk subpopulation. Initiate a systemwide collaborative effort to address disparities in care (initiation of inhaled corticosteroid [ICS], [17] ensuring follow-up after hospitalization and emergency care, [18] management of comorbid conditions). Consider education or electronic decision support as interventions for a quality improvement project to reduce disparities in care.
- Use machine learning to analyze large data sets (eg, all ED visits, [19] asthma registry) to identify associations between risk factors and poor asthma outcomes previously not considered. Collaborate with local resources to mitigate risk (legal aid to assist with poor housing, care coordination to ensure medications prescribed are covered and there is subspecialty follow-up).

PATHOPHYSIOLOGY

Asthma is a highly complex, immune-mediated, inflammatory disease, with intermittent and reversible lower airway

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obstruction due to smooth muscle constriction and airway narrowing in response to an environmental trigger, often in association with a viral upper airway infection. Numerous inflammatory pathways to airway swelling result in the many clinical phenotypes of pediatric asthma.

Longitudinal studies attempting to further understand the natural history of asthma have identified 3 distinct phenotypes: transient early wheezing, nonatopic wheezing, and atopy-associated wheezing. (20) Transient early wheezing is characterized by resolution of wheeze by 3 years of life, a lack of association with family history of asthma or early allergic sensitization as well as a positive association with prematurity, exposure to other children at child care, maternal smoking during pregnancy, and environmental tobacco smoke exposure during infancy. (20) Nonatopic wheezing is characterized by viral-induced wheeze during first the 2 to 3 years of life, with respiratory syncytial virus infection being associated with persistent wheeze later in life. (20) In contrast, atopic wheezing is characterized by a family history of atopy, early allergen sensitization, and a genetic predisposition for sensitization. (20) With any of these phenotypes, severe illness early in life is associated with progressive and persistent wheeze in later life. (20)

Five distinct clusters of asthma phenotypes (characterized by asthma and allergy severity, pulmonary physiology, allergy sensitization, total serum immunoglobulin E [IgE], and allergic inflammation) were recently described in a large urban longitudinal cohort from 9 cities in disadvantaged and largely minority children aged 6 to 17 years. (21) These phenotypes were distinguishable by the intensity of the allergic response. Similarly, a birth cohort study compared multiple groups with documented IgE antibody responses and found early exposure to multiple allergens predictive of asthma later in life. (22)

The significance of variation in early exposures to allergens versus microbes in children with asthma has been an area of speculation for some time. Ecologic data are suggestive of the "hygiene hypothesis" whereby countries with higher rates of early microbial exposure have decreased prevalence of asthma, and, conversely, countries with less exposure during childhood have higher rates of asthma. (23) Current understanding of cellular and molecular immunology suggests that exposures very early in life shape the development of a child's immune system to favor either a Th1 (nonallergic) or Th2 (allergic) lymphocyte predominance. (24) Theoretically, if a child is exposed to various microbes early in life, the immune system will favor a nonallergic, infection-fighting, ie, healthy, response. On the other hand, if a child is not exposed to many microbes and is instead exposed to certain allergens (eg, dust, mold, animal dander) the immune system will favor an allergic, inflammatory, ie, unhealthy, response. Studies support that children exposed to microbes early in life (living on farms, with older siblings or pets) have a lower risk of developing persistent wheeze later in life. Thus, the microbiome may be the intermediary step between the genetic risk of the host and clinical phenotype in asthma, and perhaps the key to primary prevention of asthma. (25)

Furthermore, allergen exposure and viral infections act synergistically in the development of asthma. (26) Children with asthma, or at risk for asthma, sensitized and exposed to perennial allergens (ie, dust, mold, mouse, rat, or cockroach), often experience airway inflammation when infected with rhinovirus. (27) Rhinovirus (subtype C) has specifically been implicated in connection with development of asthma and asthma exacerbation. (27)(28)

Cytokine-mediated inflammation in allergic asthma is the most important recent discovery in asthma pathogenesis. The airways of a sensitized child with asthma release mediators, damaging the epithelium. Th2 lymphocytes trigger the release of cytokines (interleukin [IL]-4, IL-5, IL-9, IL-13, among others), which upregulate or downregulate other cytokine receptors. (29)(30) Cytokines stimulate IgE production, mast cells, basophils, and eosinophils, which mediate inflammation via histamine, prostaglandins, and leukotrienes. (30) Newer therapies interrupt the inflammatory pathway by inhibiting the actions of specific mediators (IgE and IL-5).

Mechanistic analysis at an individual's cellular level could help guide targeted therapy. A precision medicine approach could reduce morbidity in disproportionately affected subgroups. (31) A recent study identified pro-inflammatory monocytes and type 2 cytokine activity to be more commonly associated with poorly controlled asthma in socioeconomically disadvantaged children than children with a higher socioeconomic status after controlling for potential confounders (age, sex, racial group, BMI, asthma severity, and medication use). These children also had reduced expression of genes that coded for interferon. (32) Lower levels of interferon have previously been associated with increased viral-induced exacerbations. (33)(34)(35)

TRIGGERS

Respiratory viral infections are the most common triggers of asthma exacerbation in children. (36)(37) Annual fall increases in asthma exacerbation, or the *September epidemic,* occur when many children returning to school have asthma exacerbations triggered by rhinovirus infection. (38)(39) Specific viral infections have also been found to be

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associated with increased exacerbation severity (rhinovirus [subtype C] [27] and influenza A [H1N1] [40]) and treatment failure (respiratory syncytial virus, influenza, and parainfluenza). (41) A study of influenza-related pediatric deaths between 2000 and 2016 found that 12% had asthma. (42) Annual influenza vaccination for children with asthma is considered best practice and is recommended for patients with asthma. (43) The 2018-2019 recommendations from the Advisory Committee on Immunization Practices recommend against use of the live attenuated influenza vaccine (LAIV) in children aged 2 through 4 years who have a diagnosis of asthma or have had a wheezing illness in the preceding 12 months due to a concern that the LAIV could induce exacerbation. (44) Although the 2018-2019 LAIV guidelines have not been changed, new evidence from a large trial showed improved protection and no increased risk of exacerbation with the LAIV in children with asthma. (45) Of note, the 2017-2018 and 2018-2019 American Academy of Pediatrics guidelines did not recommend the LAIV as the primary choice of influenza vaccination for all children 6 months and older owing to concerns of decreased effectiveness of the LAIV against influenza A/H1N1 in past seasons and uncertainty regarding its effectiveness this season. (46) Recently published 2019-2020 American Academy of Pediatrics guidelines, consistent with Centers for Disease Control and Prevention (CDC) recommendations, advise patients to get the LAIV. To be clear, however, details regarding recommendations for patients with asthma have not been released.

Other triggers can be organized into several categories. First, irritants bother any airway and can induce bronchospasm when a child with asthma is exposed. These include environmental tobacco smoke (47)(48)(49) and other burnt substances (candles, incense, marijuana, and electronic cigarettes); air pollution, particulate matter (fractions of particles with an aerodynamic diameter smaller than 2.5 and 10 μm), and ozone (50); chemicals in certain cleaning products; particles in the air (construction sites, perfumes, paints, soaps); and wood or charcoal fires. Allergens are specific to the child and trigger asthma in children with atopy, sometimes referred to as *allergic asthma*. These are divided into perennial allergens (mold spores, cockroaches, rats, mice, dust mites, and pet dander) and seasonal allergens (tree, weed, and grass pollens).

Weather (rapid changes or extreme cold/hot air) and strong emotions (laughter, crying, or anger) are other common triggers of bronchospasm in children with asthma. Also, medications such as β-blockers, aspirin, and nonsteroidal anti-inflammatory drugs are associated with inducing asthma exacerbations in a subset of the population.

Last, exercise and other strenuous activity are frequent triggers. Exercise-induced symptoms are more common with poorly controlled asthma. (43) Preexercise preventive short-acting inhaled β_2-agonist (SABA) with or without a step-up in asthma control is standard management. (43) Exercise-induced asthma is a rare, often overdiagnosed phenotype, where a child wheezes or coughs only after a short period of vigorous activity and symptoms improve 20 to 30 minutes after cessation of activity. Other comorbid conditions, such as severe uncontrolled allergic rhinitis, obesity, and vocal cord dysfunction, should be considered when evaluating exercised-induced symptoms. Vocal cord dysfunction, or paradoxical vocal cord motion on inspiration, typically presents with the following distinguishing features: rapid onset and offset, usually minutes to seconds; dyspnea reported on inspiration (or inspiration and expiration); patient localization of the throat and not the chest as the source of discomfort; SABA or rescue inhaler usually reported as not helping; symptoms induced by stress, anxiety, aerobic exercise, or irritants; and a flow-volume loop with a classic appearance, ie, a truncated inspiratory flow loop with a normal expiratory loop.

Another entity often confused with asthma is exercise-induced laryngeal obstruction (EILO). Any concern for vocal cord dysfunction and EILO should prompt referral to otolaryngology for further testing. Continuous laryngoscopy during exercise is the gold standard for diagnosis of EILO.

Families should be counseled on trigger identification and avoidance at routine visits for asthma care. Efforts should be made to mitigate exposure to perennial allergens (mold spores, dust mites, animal dander, cockroaches, rats, and mice) for patients with asthma with evidence by clinical history (symptoms with exposure) and allergen sensitization on skin prick testing or from serum specific IgE measurements. The following is a list of recommendations by allergen:

- Dust mites—provide mattress and pillow encasements, (51) vacuum twice a week, consider removal of carpet in the bedroom if there are significant nighttime symptoms, remove any stuffed animals from the child's bed or recommend machine washing of stuffed animals in hot water
- Mold spores—avoid humidifier use; remediate any water damage/mold in the home
- Pests—keep food out of the bedroom and in closed trash containers, exterminate if needed (preference of traps over sprays)
- Animal dander—consider removal of animal if that is an option or recommend special hypoallergenic breeds

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Environmental triggers are a major contributor to health disparities in pediatric asthma. (6) Removal of allergens in homes of children younger than 6 years with associated asthma could reduce asthma risk by 40%. (52) In addition, poor mental health is associated with poor asthma control. (53)(54) A thorough approach to potential exposures includes care coordination of appropriate referrals (allergist, nutritionist, gastroenterologist, otolaryngologist, mental health consultant), connection to community partners (local organizations that conduct home visits, provide vacuums or mattress and pillow encasements; local housing authority; 1-800-QUITLINE or other smoking cessation assistance), legal advocacy (legal aid to assist the family in advocating for housing remediation if the landlord is not being compliant with housing regulations, local law schools may also have free legal services), social work, and close follow-up for at-risk children. Tailored, comprehensive interventions reduce asthma morbidity rates in at-risk children. (15)(18)(55)(56)

CLINICAL ASPECTS

Diagnosis

Asthma in children remains largely a clinical diagnosis. A child with a family history of asthma presenting with episodic and recurring chest tightness, cough, difficulty breathing, or wheeze in response to common triggers who also demonstrates improvement with a SABA likely has asthma. In older children, demonstration of reversible bronchospasm on pulmonary function testing (PFT) is diagnostic for asthma.

The diagnosis of asthma in younger children remains challenging. Children younger than 5 years are unable to provide the effort required to reliably obtain PFT results. The Asthma Predictive Index is a clinical tool sometimes applied to children 3 years and younger with wheezing to assist with treatment and prediction of asthma. A combination of major criteria (doctor-diagnosed parental asthma or eczema) and minor criteria (doctor-diagnosed allergic rhinitis, wheezing without viral upper respiratory tract infections, or peripheral eosinophilia ≥4%) help determine risk. (57) In the original cohort, a child with wheezing and either 1 major or 2 minor criteria was 2 to 5 times more likely to have active asthma at age 6 to 13 years and 4 to 9 times more likely if they had both 1 minor and 2 major criteria. (57) A recent study developed a new clinical tool, the Pediatric Asthma Risk Score, which performed better than the Asthma Predictive Index to predict mild to moderate asthma. (58) The tool is available online for clinicians to use at https://pars.research.cchmc.org/.

In addition, measuring airway inflammation using fractional excretion of nitric oxide (FeNO) may help evaluate asthma in children who have eosinophil-mediated lung inflammation. (59) However, FeNO testing is not always covered by insurance, the equipment is seldom available in the primary care office, and guidelines do not recommend routine use. (43)(60) The 2018 Global Initiative for Asthma guidelines did report on benefits in certain situations, (60) and the update for the next National Asthma Education and Prevention Program (NAEPP) guidelines has listed FeNO as 1 of 5 areas for intensive future review. (61)

Wheezing is the characteristic finding on lung auscultation in a child experiencing asthma exacerbation, but it is not specific to asthma. Wheezing results from airflow obstruction in the lower airways and is present in many other conditions. Broad differential diagnoses of wheezing should be considered for any child with an initial episode of wheeze or difficult-to-control asthma or if there is report of little or no relief of symptoms with SABA rescue. When considering an alternative diagnosis, it is important to remember that a child could still have concomitant asthma. Table 1 lists alternative diagnoses in a child with wheeze, starting with more common entities, by age, typical findings, and testing recommendations. Another approach would be to consider alternative diagnoses by system (infectious, cardiac, pulmonary, hematologic) or mechanical obstruction causing wheeze. The latter approach is helpful when eliciting a review of systems and completing a focused physical examination in a child with first-time wheeze or difficult-to-control previously diagnosed asthma. Finally, several key historical features are important to elicit to assess severity: family history of asthma/atopy or other illness, age at onset of symptoms, episodic versus persistent disease, potential triggers or exposures, responsiveness to SABA, positionality of symptoms, and systemic signs of illness (poor weight gain, fevers, fatigue, or pallor) (Fig 1). Occasionally, a dry chronic cough is the only presenting symptom of asthma in children. These children warrant a detailed history and examination, spirometry, and a trial of bronchodilators if asthma is suspected. However, cough variant asthma is rare in children, and failure to improve with bronchodilator use should prompt further investigation.

Children with poor access to primary care often use urgent or emergency care for wheezing episodes; the chronic and recurrent nature of symptoms may lead to a delayed or missed asthma diagnosis. (63)

Diagnostic Testing/Adjuncts in Asthma

Peak Flows. Measurement of peak expiratory flow (PEF) is portable and relatively inexpensive and provides families of children older than 5 years with objective data to initiate rescue medications. A child should determine his or her personal best (the best of 3 measurements performed daily

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TABLE 1. **Differential Diagnosis of Asthma by Age and Characteristic Findings**

DIAGNOSIS	AGE	FINDINGS THAT DIFFERENTIATE FROM ASTHMA	DIAGNOSTIC TESTS
Bronchiolitis	<24 mo	No atopy, typically not responsive to SABA, context of fever and viral respiratory tract infection	Clinical diagnosis
Viral-induced wheeze	Any age (<4 y more common)	Wheezing only with viral respiratory tract infections, less atopy; usually resolves by age 4 y (62)	PFT if frequent or severe
Bronchopulmonary dysplasia	<24 mo	Symptoms since birth in premature infant	Clinical diagnosis
Chronic aspiration/GERD	Any	Chronic cough especially after meals, gastrointestinal symptoms	Gastroenterology referral, endoscopy, pH probe
Tracheomalacia/ bronchomalacia	<24 mo	Symptoms since birth, constant (as opposed to intermittent or triggered); stridor present with tracheomalacia	Laryngoscopy
Bronchiectasis	Any	Symptoms since birth, wet chronic cough, recurrent wheeze with focal lung findings, recurrent pneumonia in same location on CXR, sometimes with hemoptysis	Chest CT, bronchoscopy
Food allergy	Any	First-time wheeze in context of new food exposure and other signs of food allergy (lip swelling, vomiting, hives, hypotension)	Allergy testing, PFT
Anxiety/panic attack	School age or older	No wheezing, no improvement with SABA	Clinical diagnosis, PFT results normal
Vocal cord dysfunction	Adolescent +	Acute onset of symptoms within minutes of exercise or exposure to an irritant, symptoms quickly resolve and do not respond to SABA, sensation of airway closing, throat tightness, no symptoms during sleep; occasionally will hear inspiratory stridor on examination; hoarse voice	PFT shows classic pattern of dynamic airflow obstruction: laryngoscopy
Heart failure	Any	Fever (viral myocarditis), missed congenital heart disease, failure to thrive, symptoms worsen with feeding in young infant or with laying down; murmur, poor central pulses, hepatomegaly, crackles	Echocardiography, electrocardiography, CXR
Foreign body aspiration	<4 y (could be any age)	Acute onset of symptoms, unilateral findings, history of choking spell	Anteroposterior/posteroanterior or bilateral decubitus CXR; bronchoscopy
Mass effect (from vascular anomaly or tumor)	Any	Unilateral wheeze or stridor (may be positional, if due to a mass, ring, or sling around upper airways), symptoms worse with laying down; weight loss and other systemic signs if oncologic	Chest CT, bronchoscopy
Underlying immunodeficiency	Any	Recurrent bacterial pneumonia	CXR, immunology evaluation
Allergic bronchopulmonary aspergillosis	Any	Difficult-to-control asthma symptoms, chronic cough and intermittent fevers	Sputum, *Aspergillus* IgE and IgG, CXR
Cystic fibrosis	Any	Failure to thrive (may still have a normal newborn screen)	Sweat chloride testing, genetic testing

CT=computed tomography, CXR=chest radiography, GERD=gastroesophageal reflux disease, IgE=immunoglobulin E, IgG=immunoglobulin G, PFT=pulmonary function testing. SABA=short-acting inhaled β_2-agonist.

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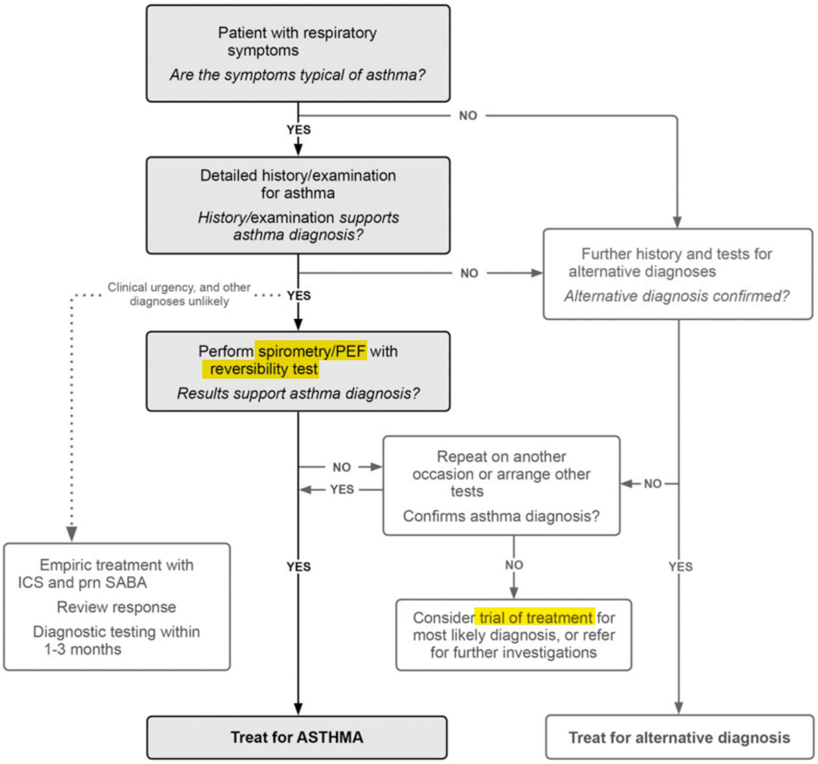
for 2 weeks) and use this number to guide acute management. (43) If the PEF falls below 80% of the child's personal best, the child or caregiver should initiate rescue medications per the asthma action plan. Generally, 70% to 80% of personal best is equivalent to yellow zone management of asthma, and 40% to 70% is equivalent to red zone management (Tables 2 and 3, Fig 2). (43) In practice, specialists who have access to in-office spirometry sometimes correlate a patient's PFT to PEF and use that to guide the determination of a child's personal best. If a child does not know his or her personal best, charts based on age and height can be used to provide general ranges. Symptoms (cough, shortness of breath, exercise intolerance) correlate with PEF and should be used to guide acute management, especially in younger children who are not able to reliably measure their PEF. When teaching patients how to use a peak flow meter, it is important to demonstrate and ask that a tight seal is made with the lips around the mouthpiece. After forcefully inhaling in, the child forcefully exhales with 1 quick breath to measure his or her PEF. Limitations of PEF include poor reliability between devices, high dependence on patient effort, and inability to detect small airway obstruction. Therefore, patients should use the same peak flow meter each time, and technique should be reviewed frequently.

PFT/Spirometry. PFT is recommended in children older than 5 years for routine management of asthma and when the diagnosis is in question. PFT is more accurate than PEF. The 2 readings important in the diagnosis and evaluation of asthma are forced expiratory volume in 1 second (FEV$_1$) and the ratio of FEV$_1$ to forced vital capacity or FEV$_{1\%}$. FEV$_{1\%}$ is the proportion of forced vital capacity a child is able to expire in 1 second. The goal of PFT in asthma is to document expiratory flow limitation or obstruction with reversibility. An FEV$_{1\%}$ of less than 0.80 is diagnostic for airflow obstruction, and reversibility with administration of a bronchodilator is diagnostic for asthma. If a child is able to fully cooperate, an FEV$_{1\%}$ greater than 0.8 is normal. The classic flow-volume curve for asthma shows a dampening and scooping out of the expiratory curve. Periodic spirometry measurements can also be helpful to measure lung function because a primary goal of asthma is to maintain healthy lung function.


Patient with respiratory symptoms
Are the symptoms typical of asthma?
YES
NO
Detailed history/examination for asthma
History/examination supports asthma diagnosis?
Clinical urgency, and other diagnoses unlikely
YES
NO
Further history and tests for alternative diagnoses
Alternative diagnosis confirmed?
Perform spirometry/PEF with reversibility test
Results support asthma diagnosis?
NO
YES
Repeat on another occasion or arrange other tests
Confirms asthma diagnosis?
NO
Empiric treatment with ICS and prn SABA
Review response
Diagnostic testing within 1-3 months
YES
NO
YES
Consider trial of treatment for most likely diagnosis, or refer for further investigations
Treat for ASTHMA
Treat for alternative diagnosis

ICS: inhaled corticosteroids; PEF: peak expiratory flow (highest of three readings). When measuring PEF, use the same meter each time as the value may vary by up to 20% between different meters; prn: as-needed; SABA: short-acting beta$_2$-agonist.
Bronchodilator reversibility may be lost during severe exacerbations or viral infections, and in long-standing asthma. If bronchodilator reversibility is not found at initial presentation, the next step depends on the availability of tests and the clinical urgency of need for treatment.

Figure 1. Diagnosis of asthma: basic approach to a child with respiratory symptoms consistent with asthma. ©2019 Global Initiative for Asthma, available from www.ginasthma.org [ginasthma.org], reprinted with permission.

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TABLE 2. **Asthma Medications (Quick Relief) (43)**

MEDICATION	DOSING RECOMMENDATION	NOTES
INH Short-Acting β_2-Agonists (to relax the smooth muscles; activates β_2 adrenergic receptors in the lungs, resulting in bronchodilation)		
Albuterol MDI (90 μg/puff; 200 puffs/canister)	Preexercise dosing: 2 puffs INH 15 min before exercise For single dose (yellow zone management on AAP): 2–4 puffs INH every 4–6 h as needed for symptoms For acute exacerbation (red zone management on AAP): 4–8 puffs every 20 min × 3 doses: ≥5 to <10 kg: 4 puffs INH every 20 min for 3 doses ≥10 to <30 kg: 6 puffs INH every 20 min for 3 doses ≥30 kg: 8 puffs INH every 20 min for 3 doses	Indicated for quick relief of bronchospasm or to prevent bronchospasm related to exercise Adverse effects include tachycardia and tachypnea
Albuterol inhalation solution (0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL, or 5 mg/mL)	≥5 to <30 kg: 2.5-mg neb INH for single dose OR 7.5-mg neb INH for 1 h ≥30 kg: 5-mg neb INH for single dose OR 15-mg neb INH for 1 h If still wheezing and in distress after 2 h of short-acting β_2-agonist, consider continuous neb treatment (0.6 mg/kg per hour): ≥5 to <10 kg: 5-mg/h neb INH every 1 h ≥10 to <20 kg: 10-mg/h neb INH every 1 h ≥20 to <30 kg: 15-mg/h neb INH every 1 h ≥30 kg: 20-mg/h neb INH every 1 h	
Anticholinergics (antimuscarinic agent [blocks action of acetylcholine], which results in decreased contractility of smooth muscle resulting in bronchodilation)		
Ipratropium bromide inhalation solution (0.25 mg/mL)	0.25–0.5 mg neb INH every 20 min for 3 doses ≥5 to <30 kg: 0.5 mg neb INH once 30 kg: 1 mg neb INH once	Indicated in the ED setting for moderate to severe exacerbation Can cause transient dilation of the pupil(s) and blurry vision if neb formulation is blown into the eyes for a prolonged period
Ipatropium bromide MDI (18 μg/puff)	4–8 puffs every 20 min INH for 3 doses	
Systemic Corticosteroids (anti-inflammatory; reverses B2-receptor downregulation)		
Dexamethasone	Short course (burst): ≥7 to <10 kg: 6 mg PO once with repeat dose in 24 h ≥10 to <20 kg: 10 mg PO once with repeat dose in 24 h ≥30 kg: 16 mg PO once with repeat dose in 24 h OR 0.6 mg/kg IV or IM (max, 16 mg) in children not tolerating oral medications	Indicated for treatment of moderate to severe exacerbations
Prednisone (1-, 2.5-, 5-, 10-, 20-, and 50-mg tablets)	Short course (burst): 1–2 mg/kg per day PO (max, 60 mg) for 3–10 d divided twice daily	Consider comorbidities, eg, studies show patients with sickle cell disease and asthma have rebound acute chest syndrome with systemic corticosteroids and, hence, should be avoided (64)
Prednisolone (5 mg/5 mL or 15 mg/5 mL)	Short course (burst): 1–2 mg/kg per day PO (max, 60 mg) for 3–10 d divided twice daily	Will raise serum glucose so use with caution in diabetes
Methylprednisolone	Short course (burst): 1–2 mg/kg per day IV (max, 60 mg) for 3–10 d divided every 6–12 h	
Adjunct acute asthma medications		
Magnesium sulfate	50 mg/kg per dose (max, 2,000 mg/dose) IV once over 20 min	Consider after 1 h of short-acting β_2-agonists and after systemic corticosteroids if still with respiratory distress and wheezing

Continued

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TABLE 2. (Continued)

MEDICATION	DOSING RECOMMENDATION	NOTES
Epinephrine (1:1,000) (1 mg/mL)	0.01 mg/kg per dose (max, 0.5 mg/dose) IM once	Consider in severe, life-threatening asthma

AAP=asthma action plan, ED=emergency department, h=hour, INH=inhaled, IM=intramuscular, IV=intravenous, max=maximum, MDI=metered-dose inhaler, neb=nebulized, PO='per os' or by mouth.

Methacholine Challenge. Bronchoprovocation tests, such as the methacholine challenge, are not a common practice in pediatrics and are usually performed only by specialists. In addition, methacholine challenge testing has high negative predictive power and, hence, performs well in establishing the lack of asthma, or ruling out disease. (66)

Impulse Oscillometry. Impulse oscillometry is a newer PFT that allows for passive measurement of lung function. It is useful for children as young as 3 years and other children who have difficulty with traditional PFT because minimal effort is required by the child. (67) However, impulse oscillometry is only available in a pulmonologist's office.

Chest Radiography. Chest radiographs are low yield in the acute setting and rarely change management. However, obtaining a radiograph should be considered when a child presents with hypoxia and high fever and is not improving on albuterol and systemic corticosteroids. (68)

Furthermore, a chest radiograph may be indicated at the first presentation of wheeze or when considering alternative diagnoses other than asthma (Table 1).

Management

The overall goal in managing asthma in children is to reduce impairment (maintaining a good quality of life, allowing for normal activities without limitation, and reducing missed school days) and to reduce risk (keeping children off systemic corticosteroids, out of the hospital and ED, and maintaining healthy lung function to prevent airway remodeling that is associated with chronic inflammation).

Severity Classification

The NAEPP guidelines, last revised in 2007, set age-based criteria to standardize the classification and management of asthma. The guidelines for classification are based on the magnitude of a child's risk (occurrence of acute severe exacerbations in the past 12 months) and impairment (day-to-day symptoms over the past 4 weeks). Based on risk and impairment, asthma is classified into intermittent, mild persistent, moderate persistent, and severe persistent. Control, using similar assessments of risk and impairment, should be assessed every 3 months at routine asthma visits and is classified as well controlled, not well controlled, or very poorly controlled. Figure 2 details the current approach to initial assessment of disease severity and ongoing assessment of control. Classification and control designation of asthma guides should be made at each visit per NAEPP guidelines.

Longitudinal Care

Once asthma severity and level of control have been determined, the guidelines specify initial therapy or change of therapy in a stepwise manner. (43) The mainstay of asthma therapy consists of bronchodilators (ie, SABA) for rescue therapy to relax the smooth muscles surrounding the airway (bronchodilation) and corticosteroids to help reduce inflammation inside the airway. A routine asthma visit should be scheduled every 3 to 6 months. Barriers to asthma control, adherence, and demonstration of proper medication administration should be assessed and addressed at each visit. Treatment decisions should be based on recommended step level only after adherence has been assessed and triggers have been identified in conjunction with a plan for trigger modification/avoidance (Fig 2). (69)

Management of chronic asthma can be confusing for children and families. Education should be provided using lay terminology. Visual aids to illustrate narrowed airways and explain which medications reverse bronchospasm and offer quick relief (SABAs) versus reduce and control inflammation (corticosteroids or leukotriene receptor antagonists [LTRAs]) are helpful. A misunderstanding in the difference between quick-relief medications and daily controller medications is a common barrier to adherence (Tables 2 and 3). The instructions should be clear, communicated verbally and in writing (with a detailed asthma action plan), and reinforced at each visit. A typical asthma action plan is divided into 3 sections. The green zone provides instructions on routine medications (ICSs, LTRAs, preexercise SABAs, allergy medications). The yellow zone provides instructions about home management of acute, mild

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TABLE 3. Asthma Medications (Maintenance or Controller Medications) (65)

MEDICATION	DAILY DOSE, BY AGE 0–4 Y	5–11 Y	≥12 Y	ADVERSE EFFECTS
Leukotriene modifiers				
Montelukast (leukotriene receptor antagonist) 4- or 5-mg chewable tablet 4-mg granules or 10-mg tablet	(1–5 y): 4 mg by mouth once before bedtime (6–14 y): 5 mg by mouth once before bedtime (>14 y): 10 mg by mouth once before bedtime			
Immunomodulators				
Omalizumab (anti-IgE) SC injection, 150 mg/1.2 mL, after reconstitution with 1.4 mL of sterile saline	NA	≥6 y: 150–375 mg SC every 2–4 wk (depends on bodyweight and pretreatment serum IgE levels)	150–375 mg SC every 2–4 wk (depends on bodyweight and pretreatment serum IgE levels)	Pain and bruising at injection sites Risk of anaphylaxis (0.2%)
Long-acting muscarinic antagonist				
Tiotropium bromide*2.5 μg (2 actuations; 1.25 μg/actuation)	NA	≥6 y: 2 actuations inhaled daily	2 Actuations inhaled daily	Caution with use if creatinine clearance <60 ml/min
Inhaled corticosteroids				
Beclomethasone HFA: 40 or 80 μg/puff	NA	(L): 80–160 μg (M): >160–320 μg (H): >320 μg	(L): 80–240 μg (M): >240–480 μg (H): >480 μg	Must rinse mouth after each use to prevent oral thrush and systemic absorption
Budesonide DPI: 90 or 180 μg/inhalation	NA	(L): 180–360 μg (M): 360–720 μg (H): >720 μg	(L): 180–540 μg (M): 540–1080 μg (H): >1,080 μg	
Budesonide nebules: 0.25, 0.5, or 1 mg	(L): 0.25–0.5 mg (M): >0.5–1 mg (H): >1 mg	(L): 0.5 mg (M): 1 mg (H): 2 mg	NA	
Flunisolide HFA: 80 μg/puff	NA	(L): 160 μg (M): 320–480 mg (H): ≥480 μg	(L): 320 μg (M): >320–640 μg (H): >640 μg	
Fluticasone HFA/MDI: 44, 110, 220 μg/puff	(L): 176 μg (M): >176–352 μg (H): >352 μg	(L): 88–176 μg (M): >176–352 μg (H): >352 μg	(L): 88–264 μg (M): >264–440 μg (H): >440 μg	
Fluticasone DPI: 50, 100, or 250 μg/inhalation	NA	(L): 100–200 μg (M): >200–400 μg (H): >400 μg	(L): 100–300 μg (M): >300–500 μg (H): >500 μg	
Mometasone DPI: 110 μg, 220 μg/inhalation HFA: 100 μg, 200 μg/puff	NA	(L): 110 μg (M):>220–440 μg (H): >440 μg	(L): 100–220 μg (M): >200–440 μg (H): >440 μg	

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TABLE 3. (Continued)

MEDICATION	DAILY DOSE, BY AGE 0–4 Y	5–11 Y	≥12 Y	ADVERSE EFFECTS
Inhaled corticosteroid + long-acting B_2-agonist (combination medications)				
Fluticasone/salmeterol DPI: 100 mcg/50 µg, 250 mcg/50 µg, or 500 mcg/50 µg HFA: 45 mcg/21 µg, 115 mcg/21 µg, 230 mcg/21 µg	NA	1 Inhalation BID Not well controlled and on low- to medium-dose ICS: 100/50 DPI or 45/21 HFA Not well controlled and on medium- to high-dose ICS: 250/50 DPI or 115/21 HFA		Must rinse mouth after each use to prevent oral thrush
Budesonide/formoterol HFA MDI: 80 mcg/4.5 µg, 160 mcg/4.5 µg	NA	Not well controlled and on low- to medium-dose ICS: 80/4.5 Not well controlled and on medium- to high-dose ICS: 160/4.5		
Mometasone/formoterol MDI: 100 µg/5 mcg	NA	NA	2 Inhalations BID (depends on asthma severity)	

Doses are per National Asthma Education and Prevention Program update in September 2012 except for (*). Source: National Heart, Lung, and Blood Institute; National Institutes of Health; US Department of Health and Human Services. BID=twice a day, DPI=dry powder inhaler, (H)=high daily dose, HFA=hydrofluoroalkane, ICS=inhaled corticosteroid, IgE=immunoglobulin E, (L)=low daily dose, (M)=medium daily dose, MDI=metered-dose inhaler, NA=not available (not approved, no data available, or safety and efficacy not established in this age group), SC=subcutaneous.

exacerbations with escalation to red zone management while seeking emergency medical care. Children with persistent asthma should be seen every 3 months to assess ongoing control and to adjust controller medications. Providing tools (smartphone alarms, mobile applications, or simply placing the daily inhaler and spacer next to the toothbrush) may improve adherence. (70)

Adherence to medication is also affected by improper delivery. Spacer use with a demonstration of appropriate technique should be assessed at each visit. All patients, regardless of age, should use a spacer when using a metered-dose inhaler rescue or controller medication. The spacer ensures delivery of the medication to the lungs and reduces medication that deposits inside of the mouth with subsequent systemic absorption. Both mask and mouthpiece spacer should be appropriate, and the choice is mostly based on age and ability to demonstrate proper technique. Exceptions for spacer use include new devices that either have a built-in spacer and devices with specific instructions to not use a spacer (this should be included in the package insert). All children taking controller ICSs should rinse their mouth after use to prevent oral thrush and to minimize systemic absorption. A video demonstrating proper spacer technique is available online (https://vimeo.com/channels/impactdc).

Frequent introductions of new delivery systems for asthma medications are common with changes in insurance formularies and the availability of new devices on the market. Providers must be vigilant to ensure insurance coverage of prescribed medications and should check manufacturer websites for online videos to familiarize themselves with proper technique of new devices to teach their patients.

Finally, it is crucial to assess parent and adolescent "buy-in" to chronic medication use. For a parent, it helps to explain the process inside the lungs in the context of therapeutic effect and potential for airway remodeling (71) if chronic uncontrolled asthma persists. For an adolescent, the consequences have to be more immediate, ie, the ability to perform better at their specific sport or extracurricular activity with regular use of controller medications.

Persistent asthma requires a thorough and ongoing assessment of potential comorbid conditions. Addressing potentially treatable comorbidities commonly seen with childhood asthma (obesity, [72] obstructive sleep apnea, allergic rhinitis, gastroesophageal reflux, and stress or depression) could avoid unnecessary escalation of asthma therapy. A complete review of symptoms should reveal these diagnoses.

Finally, when prescribing controller medications, the provider should ensure patient access to medications. In addition to assessing insurance coverage of the ICS brand, a

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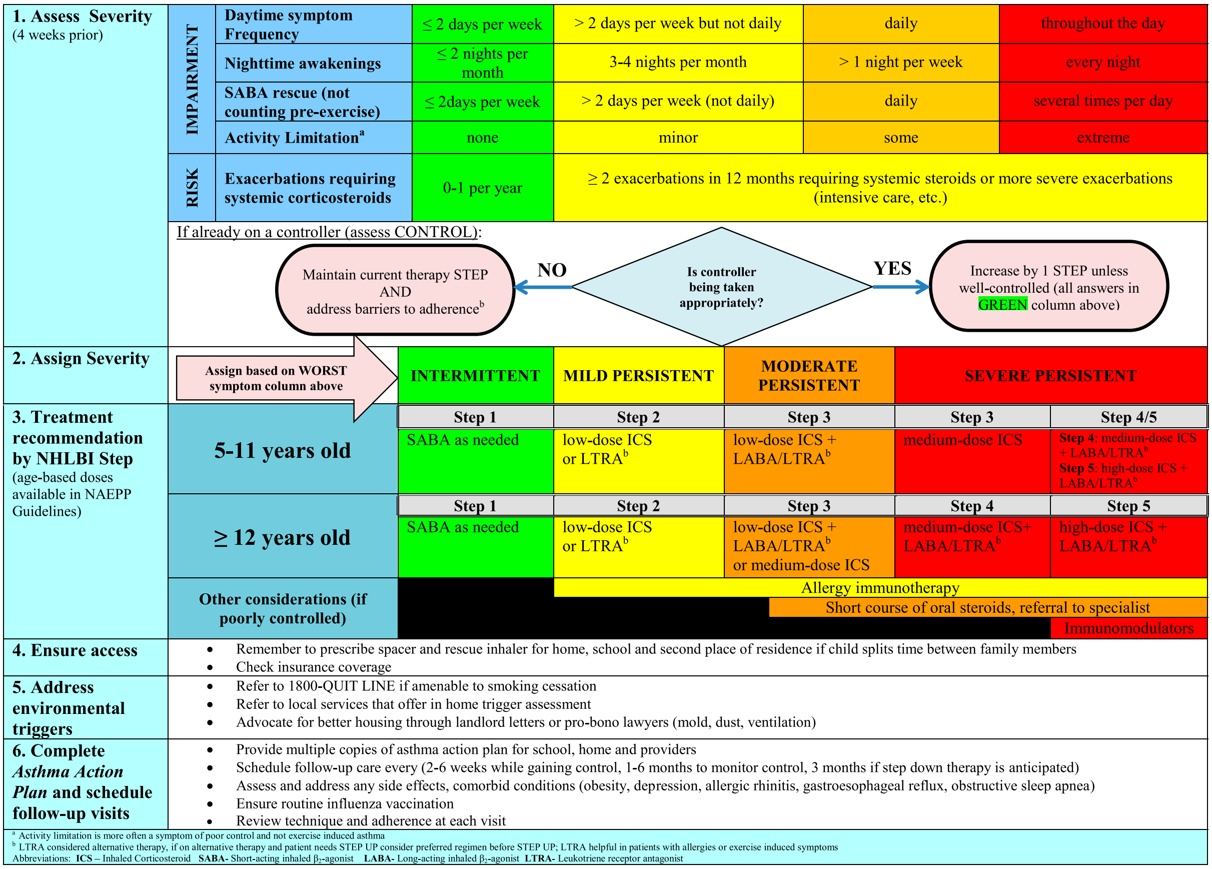

1. Assess Severity (4 weeks prior)	**IMPAIRMENT**	**Daytime symptom Frequency**	≤ 2 days per week	> 2 days per week but not daily	daily	throughout the day
		Nighttime awakenings	≤ 2 nights per month	3-4 nights per month	> 1 night per week	every night
		SABA rescue (not counting pre-exercise)	≤ 2days per week	> 2 days per week (not daily)	daily	several times per day
		Activity Limitation^a	none	minor	some	extreme
	RISK	**Exacerbations requiring systemic corticosteroids**	0-1 per year	≥ 2 exacerbations in 12 months requiring systemic steroids or more severe exacerbations (intensive care, etc.)		

If already on a controller (assess CONTROL):

Is controller being taken appropriately?

NO → Maintain current therapy STEP AND address barriers to adherence^b

YES → Increase by 1 STEP unless well-controlled (all answers in GREEN column above)

2. Assign Severity	**Assign based on WORST symptom column above**	**INTERMITTENT**	**MILD PERSISTENT**	**MODERATE PERSISTENT**	**SEVERE PERSISTENT**	
3. Treatment recommendation by NHLBI Step (age-based doses available in NAEPP Guidelines)	**5-11 years old**	**Step 1**	**Step 2**	**Step 3**	**Step 3**	**Step 4/5**
		SABA as needed	low-dose ICS or LTRA^b	low-dose ICS + LABA/LTRA^b	medium-dose ICS	**Step 4**: medium-dose ICS + LABA/LTRA^b **Step 5**: high-dose ICS + LABA/LTRA^b
	≥ 12 years old	**Step 1**	**Step 2**	**Step 3**	**Step 4**	**Step 5**
		SABA as needed	low-dose ICS or LTRA^b	low-dose ICS + LABA/LTRA^b or medium-dose ICS	medium-dose ICS+ LABA/LTRA^b	high-dose ICS + LABA/LTRA^b
	Other considerations (if poorly controlled)		Allergy immunotherapy			
				Short course of oral steroids, referral to specialist		
						Immunomodulators

4. Ensure access	• Remember to prescribe spacer and rescue inhaler for home, school and second place of residence if child splits time between family members • Check insurance coverage
5. Address environmental triggers	• Refer to 1800-QUIT LINE if amenable to smoking cessation • Refer to local services that offer in home trigger assessment • Advocate for better housing through landlord letters or pro-bono lawyers (mold, dust, ventilation)
6. Complete *Asthma Action Plan* and schedule follow-up visits	• Provide multiple copies of asthma action plan for school, home and providers • Schedule follow-up care every (2-6 weeks while gaining control, 1-6 months to monitor control, 3 months if step down therapy is anticipated) • Assess and address any side effects, comorbid conditions (obesity, depression, allergic rhinitis, gastroesophageal reflux, obstructive sleep apnea) • Ensure routine influenza vaccination • Review technique and adherence at each visit

[a] Activity limitation is more often a symptom of poor control and not exercise induced asthma

[b] LTRA considered alternative therapy, if on alternative therapy and patient needs STEP UP consider preferred regimen before STEP UP; LTRA helpful in patients with allergies or exercise induced symptoms

Abbreviations: **ICS** – Inhaled Corticosteroid **SABA-** Short-acting inhaled β_2-agonist **LABA-** Long-acting inhaled β_2-agonist **LTRA-** Leukotriene receptor antagonist

Figure 2. Asthma control, severity classification, and treatment flow diagram for children 5 years and older. (43)(69)

family's ability to pay or afford the co-pay should be considered. Privately insured families with limited additional funds may qualify for coupons available on the manufacturer's website. Also, if possible, one should obtain prior authorizations for additional spacers and rescue inhalers for school and multiple residences because a child may live in multiple households. Routine follow-up appointments should be scheduled at the time of visits, and the importance of these visits with plans for step-up or step-down therapy should be communicated to families. Addressing barriers, (73) coordinating care, (15) and ensuring adherence to guideline-based care (74) are imperative for reducing disparities in asthma care.

Allergy testing for indoor allergens (certain molds, animal dander, house dust mites, and cockroach) is recommended for patients with persistent asthma and reported exposure to allergens. (43)(60) Guidelines recommend targeted skin prick testing because it is low cost and accurate, and targeted serum specific IgE if a child is uncooperative. (60) In practice, it is important to obtain a clinical history of allergen exposure because any report of asthma symptoms in reference to an exposure supersedes allergy testing results, and allergen avoidance should continue to be recommended.

In addition, children with severe allergic rhinitis may benefit from subspecialist referral to an allergist for consideration of specific and targeted immunotherapy. Current evidence supports in-office subcutaneous immunotherapy for single allergens in children with persistent asthma and a clear relationship between symptoms and exposure to a specific allergen to which the patient has documented sensitivity. Guidelines support immunotherapy for 3 specific allergens: dust mites, animal dander, and pollen. (43) Patients who receive immunotherapy are at risk for anaphylaxis and should be closely monitored. The update for the 2007 NAEEP guidelines lists immunotherapy as 1 of the 5 specific areas of future in-depth review. (61)

Severe Asthma

Immunomodulatory medications, or biological agents, are emerging treatments in children with moderate to severe asthma. If a child is taking medium- to high-dose ICS and long-acting inhaled β_2-agonist and demonstrates poor control despite proper technique and good adherence (frequent

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TABLE 4. **Recent Evidence for Emerging Trends in the Treatment of Asthma**

PRACTICE CONSIDERATION	EVIDENCE POPULATION, NO.	DESIGN	FINDINGS (LIMITATIONS)	RECOMMENDATION
School-based asthma therapy				
Halterman et al (2011) (82)	Children aged 3–10 y with asthma and Medicaid insurance (n = 530)	Prospective RCT comparing home versus school administration of ICS	School administration of ICS effectively improves adherence (performed in conjunction with dose adjustment as needed and tobacco smoke reduction program) (single site)	Recommend partnership with local school to see whether school-based asthma therapy is a feasible alternative to home-based therapy, especially for those patients with poor adherence. Consider direct delivery of medications to the school.
Fall montelukast				
Johnston et al (2007) (83)	Children aged 2–14 y with asthma (n = 194)	RCT, double-blind, placebo-controlled trial comparing a group started on age-appropriate nightly dose of montelukast from September 1 for 45 d	53% Decrease in "worse asthma symptoms" and 78% reduction in unscheduled asthma visits; boys 2–5 y and girls 10–14 y with most benefit (no minimum asthma severity for inclusion; pragmatic trial with poor adherence to ICS in study population)	Mixed results; could consider Fall montelukast in a persistent asthma population with poor ICS adherence (especially males aged 2–5 y and females aged 10–14 y)
Weiss et al (2010) (84)	Children aged 6–14 y with asthma (n = 1162)	RCT, multicenter, double blind, placebo controlled, comparing 5-mg montelukast night before day 1 of school for 8 wk; evaluated percent days with worse asthma	No difference between placebo and montelukast groups (no minimum asthma severity for inclusion)	
Preseasonal treatment with omalizumab				
Teach et al (2015) (85)	Inner-city asthmatic children aged 6–17 y with ≥1 recent exacerbations (n = 727)	3-arm RCT, double blind, double placebo controlled, multicenter	Compared to placebo, omalizumab had a significantly lower rate of fall exacerbations, and omalizumab boosted interferon levels with a decrease in rhinovirus infection in the omalizumab group	Consider the addition of omalizumab to guidelines-based therapy for inner city children, aged 6-17 y, before the fall season, especially if they have a recent history of exacerbation
Intermittent, extreme high-dose ICS dose for acute asthma				
Jackson et al (2018) (86)	Children aged 5–11 y with mild to moderate persistent asthma, with 1 course of systemic corticosteroids in previous year (n = 254)	Double-blind RCT comparing low-dose ICS with quintupled-dose ICS for 7 d at early signs of loss of asthma control	No difference between the groups in degree of asthma control	Good evidence to recommend against intermittent escalation in ICS for yellow zone management in children; however, seasonal increase may be supported in an urban setting (87)(88)

Continued

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TABLE 4. (Continued)

PRACTICE CONSIDERATION	EVIDENCE POPULATION, NO.	DESIGN	FINDINGS (LIMITATIONS)	RECOMMENDATION
McKeever et al (2018) (89)	≥16 y on any dose of ICS with ≥1 exacerbation in previous 12 mo requiring systemic corticosteroids (n = 1,922)	Pragmatic, randomized, unblinded trial comparing self-increase in ICS to 4 times the dose with those that did not increase baseline ICS dose for yellow zone management × 14 d or peak flow normal	Fewer severe exacerbations in high-dose ICS group (no children in low-dose ICS group; subject to bias and found only 19% reduction in increased ICS group) (87)(88)	* This contradicts current GINA recommendations. (60)
Decision support for guideline-based care				
Bell et al (2010) (17)	Urban primary care clinics (n = 12)	Cluster RCT trial of clinical decision support in the electronic health record	Improved primary care provider compliance with NAEPP guideline–based care (17)	Strong recommendation to consider implementation if feasible
Oral prednisolone in preschoolers with wheeze				
Panickar et al (2009) (90)	Children aged 10–24 mo hospitalized for viral-induced wheeze (n = 700)	RCT, double-blind, placebo-controlled, 5-d course of oral prednisolone	No difference in LOS of hospitalization	Good evidence to suggest against use of OCS in viral-induced wheeze
Foster et al (2018) (91)	Children aged 24–72 mo presenting to ED with viral-induced wheeze (n = 605)	RCT, double-blind, placebo-controlled, noninferiority trial, single dose of oral prednisolone to reduce ED LOS	Placebo group with longer LOS (540 min) versus prednisone group (370 min), single center, baseline very long LOS, unclear whether generalizable to different settings, unclear whether meaningful outcome studied)	
Dupilumab (anti–interleukin-4 receptor α monoclonal antibody) for moderate to severe uncontrolled asthma				
Castro et al (2018) (92)	Children aged ≥12 y, uncontrolled asthma (n = 1902)	Randomized to 4 arms to receive add on dupilumab every 2 weeks versus placebo for 1 y at 2:2:1:1 ratio	Lower rates of severe exacerbation and better lung function; results better in children with higher baseline eosinophilia	Promising results, good evidence for use of dupilumab in severe uncontrolled asthma (93)
Rabe et al (2018) (80)	Children age ≥12 y; OCS-dependent severe asthma (n = 210)	Random assignment of add-on dupilumab every 2 wk versus placebo for 24 wk in an attempt to reduce OCS dose	Improved lung function, decreased OCS dose, and fewer exacerbations in treatment group (small study)	

ED=emergency department, GINA=Global Initiative for Asthma, ICS=inhaled corticosteroid, LOS=length of stay, NAEPP=National Asthma Education and Prevention Program, OCS=oral corticosteroid, RCT=randomized controlled trial.

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TABLE 5. **Evidence-Based Management of Acute Asthma**

PRACTICE	RECOMMENDATION
Systemic corticosteroids	Supports early administration of systemic corticosteroids in moderate to severe asthma exacerbations with reduction in need for hospitalization if given within 1 h of ED presentation. (100) Oral route is preferred route, and effects are considered equivalent. (43) Short course (1–2 d) of dexamethasone equivalent to 3- to 5-d burst of prednisolone in acute asthma exacerbation. (101) Equivocal data on single versus 2 doses of dexamethasone. (102)
Bronchodilator administration	MDI with spacer equally effective as nebulized bronchodilator therapy in the ED. (103)(104) Additional benefits include cost-savings (105) and decreased ED length of stay. (106) Equivocal studies on continuous versus intermittent bronchodilator nebulization for severe asthma, GINA guidelines recommend initial continuous therapy with spacing to intermittent in severe asthma. (60)
Inhaled ipratropium bromide	Supports use in moderate to severe exacerbations with SABA in preventing need for hospitalization, (107) no additional benefit during hospitalization. (108) Not routinely recommended in mild exacerbations. (43)(60)
Intravenous magnesium sulfate	No clear support for routine use due to paucity of data; however, administration of intravenous magnesium sulfate in moderate to severe asthma exacerbations if not improving after 1 h of bronchodilator and systemic corticosteroid treatment may reduce need for admission. (43)(109) A recent trial showed potential benefit for patients with severe asthma and pulse oximetry <92%. (95) More data needed.
Epinephrine	Insufficient evidence; however, guidelines support administration for children with very poor effort unable to adequately inhale nebulized bronchodilators or possibility of anaphylaxis and in life-threatening situations. Although no significant detrimental effects either. (43)(60)
Noninvasive respiratory support	Bilevel positive airway pressure has been studied more than HFNC in the management of severe asthma exacerbation, however still with limited evidence to support or recommend against its use. (110) Insufficient data in support of HFNC in setting of asthma to recommend use. Small pilot study using HFNC for severe asthma compared it with nasal cannula oxygen with promising results. (111) Often used in ICU settings to avoid intubation.
Heliox	Consensus-based recommendation for severe exacerbations in conjunction with standard therapy, but caution to not delay intubation if needed. (43)(60) Maximum oxygen content of heliox is 30% FiO_2 and, therefore, is not recommended in patients requiring higher % FiO^2.
Terbutaline	Insufficient evidence to support use. (112) Sometimes given to children with very poor effort unable to adequately inhale nebulized bronchodilators, similar to epinephrine indicated in life-threatening situations; however, has more adverse effects than epinephrine. (43)(60)
Ketamine	Insufficient evidence for ventilated or nonventilated patients. (113)
✗ Intravenous aminophylline	Evidence recommends against use due to poor safety profile in children. (43)(60)(112)
Volatile anesthetics	Used in ICU settings in ventilated patients, not mentioned in guidelines, with insufficient evidence for routine use; no difference in outcomes in a large pediatric retrospective review. (114)
Chest radiography	Low yield in the ED and rarely changes management, consider with hypoxia and high fever if not improving on albuterol and systemic corticosteroids. (68)
ICS prescription at time of discharge from ED or admission	ICS should be initiated before ED discharge. (115) Regular use of low-dose ICS is associated with decreased risk of death from asthma. (116)

ED=emergency department, FiO_2=fraction of inspired oxygen, GINA=Global Initiative for Asthma, HFNC=high-flow nasal cannula, ICS=inhaled corticosteroid, MDI= metered-dose inhaler, SABA=short-acting inhaled β_2-agonist.

exacerbations requiring systemic corticosteroids, intensive care, or intubation), (43)(60) he or she should be referred to a specialist for treatment of severe asthma. The specialist should evaluate for other diagnoses that mimic asthma (Table 1) before consideration of asthma treatment with biological agents (anti-IgE, anti–IL-5, or anti–IL-5α). (43)(60) Omalizumab, a monoclonal antibody that binds to IgE, is recommended for difficult-to-control moderate to severe persistent asthma in children 6 years and older with elevated IgE counts. (75) In a cohort of inner-city youth aged 6 to 20 years with uncontrolled persistent asthma and elevated IgE levels, omalizumab significantly decreased fall

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exacerbations and improved overall control of asthma. (76) Mepolizumab (anti–IL-5), (77) benralizumab (anti–IL-5α), (78)(79) and dupilumab (anti–IL-4α) (80) are options for children with eosinophilia (eosinophil count >150 and 300/μL [0.15 and 0.30×10^9/L], respectively) who are 12 years and older. Early initiation of biological agents in poorly controlled moderate to severe asthma is associated with reduced hospitalizations and ED visits for asthma. (81) Newer biological agents that target different mediators of the inflammatory pathway and other emerging trends are discussed in Table 4.

Acute Asthma

The management of acute asthma includes early and repeated administration of SABA per the individual asthma action plan (usually 2–4 puffs inhaled with spacer every 4 hours in the yellow zone) at the first symptoms of bronchospasm for mild exacerbations. For moderate to severe exacerbations (red zone on the asthma action plan), the typical asthma action plan usually recommends 4 to 8 puffs inhaled with spacer every 15 minutes for 3 doses while on the way to the ED. High-dose ICS for yellow zone management of acute asthma is not effective and should not generally be recommended. (86)(89) Specific guidelines for prescribing a home supply of emergency oral corticosteroids with specific instructions for use with or without a telephone consultation with a physician do not exist. However, a small study did show decreased ED use in children with moderate to severe asthma who had a home supply of emergency oral corticosteroids. (94)

ED management of acute asthma includes prompt systemic corticosteroids and higher doses of SABA mixed with 2 to 3 doses of ipratropium bromide for moderate to severe exacerbations. It is important to assess response to therapy after 1 hour of treatment and if there is no significant improvement to consider intravenous magnesium sulfate because this has been shown to reduce risk of hospitalization. (95) SABA should be continued until there is clinical evidence of reversal of obstruction (decreased respiratory effort and rate, improved oxygenation and ventilation) (Tables 2 and 3). In addition to reversing bronchoconstriction, supportive therapies, including supplemental oxygen, intravenous fluids, or ventilatory support, should be initiated as needed. A lethargic or agitated child with asthma exacerbation may have acidosis from hypercarbia secondary to poor ventilation and would benefit from noninvasive positive pressure support or intubation. In addition, transient hypoxia secondary to ventilation-perfusion mismatch is not uncommon after treatment with bronchodilator therapy.

ED management of asthma often relies on clinical pathways using asthma severity scores to expedite initiation of treatment. (96) Multiple pediatric asthma severity scores exist, with wide variation in rigor of validation and ability to predict response to treatment. (97)(98)(99) Evidence-based management of acute asthma is discussed in Table 5.

Pharmacogenetics and Race/Ethnicity. As mentioned previously, Puerto Rican children had the highest asthma prevalence of any group until 2016, when the prevalence in black children increased to 15.7%. (3) Although it is likely multifactorial, there is some evidence of impaired response to SABAs in Puerto Rican children secondary to factors involving the β_2-adrenergic receptor genes. (117) In addition, a small cross-sectional study of children with persistent asthma compared response to SABA in Mexican American and Puerto Rican children and found improved responsiveness in Puerto Rican children when an LTRA was added. (118) Further investigation of asthma pharmacogenetics comparing children from different ethnic groups may help address health disparities in asthma.

CONCLUSION

Management of many other chronic diseases has benefited from a coordinated approach extending beyond the clinic and into the community. Quality improvement efforts should focus on improving outcomes for vulnerable children by ensuring adherence to guideline-based therapy, correct assessment of severity and control, and a coordinated approach to care. Population health approaches and novel therapies showing effectiveness in specific phenotypes present an opportunity to identify at-risk children with asthma and to begin to decrease the health disparities in childhood asthma.

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Summary

- Based on observation, health disparities in pediatric asthma exist. (4) Based on expert opinion, providers should design and implement quality improvement projects to help bridge the gap. (15)
- Based on observation, environmental triggers are a major contributor to health disparities in pediatric asthma. Working to reduce exposure to individual triggers will improve asthma control. (52)(55)
- Based on observation, complex interactions between a child's genetic risk, environment (allergen sensitization, exposure to viral infections), (26) and changes to the airway at the cellular level help predict disease and target therapy. (31)
- Based on expert opinion, always consider alternative or concomitant diagnoses in a child with new wheeze or difficult-to-control asthma. (43)(60)
- Based on moderate recommendation, guideline-based care is associated with improved outcomes in asthma. (74)
- Based on moderate recommendation, children with moderate to severe asthma often benefit from treatment with seasonal escalation of inhaled corticosteroid dose (although not higher than recommended by the National Asthma Education and Prevention Program guidelines), (43)(85) leukotriene receptor antagonist (83) or novel immunomodulatory medications (85) to reduce fall exacerbations. There seems to be no benefit from high-dose inhaled corticosteroid use for yellow zone management of acute asthma. (86)(89)

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1. You have been appointed as the president of a large pediatric health system. In looking at the system's readmission data, it was clear that asthma readmissions have one of the highest rates compared with national benchmarks. You design a strategic plan aimed at improving prevention strategies for childhood asthma in the population you serve with the goal to decrease readmissions. Although your plan should target all children admitted with asthma, in which of the following groups of children will prevention strategies have the highest impact due to their highest rates of readmission?
   - A. Asian.
   - B. Black.
   - C. White.
   - D. Hispanic.
   - E. Native American.
2. A 15-month-old girl is seen in the clinic with a 2-day history of upper respiratory tract infection symptoms, including clear rhinorrhea and cough. The patient was born at 30 weeks' gestation and was in the nursery for 6 weeks, where she received supplemental oxygen. Physical examination is significant for low-grade fever and scattered wheezes heard diffusely over both lungs. The remaining examination findings are normal. There is no family history of asthma or atopy. The patient is an only child and stays at home with mom. There are no sick contacts, and there are no pets or smokers in the house. Which of the following is the most likely natural history of wheezing in this patient?
   - A. Atopic wheezing.
   - B. Exercise-induced wheezing.
   - C. Nonatopic wheezing.
   - D. The patient will most likely be an asthmatic adult.
   - E. Transient early wheezing.
3. You are developing asthma education materials aimed at parents and school personnel. In discussing asthma triggers, which of the following is the most common trigger of asthma exacerbation in children?
   - A. Bacterial pneumonia.
   - B. Dust mite antigen.
   - C. Pet dander.
   - D. Perfumes.
   - E. Viral respiratory infections.
4. A 6-year-old boy is brought to the emergency department by his parents because he woke up from sleep with acute onset of coughing, increased work of breathing, and chest pain. The family is visiting with the grandparents, who have a dog. The grandfather smokes outside. There is no history of fever or upper respiratory tract infection symptoms. Family history is positive for allergic rhinitis in the mother. On physical examination the child is alert and awake and in moderate respiratory distress. He is coughing and seems short of breath. His pulse oximetry is 89% on room air. Lung examination shows decreased air entry diffusely with scattered wheezes bilaterally. There is no history of similar symptoms, and the family has no pets. In the emergency department he was given 3 albuterol aerosols, resulting in significant improvement. His chest radiograph is normal except for hyperinflation. Which of the following is the most appropriate test to confirm the diagnosis in this patient?
   - A. Fractional excretion of nitric oxide.
   - B. Impulse oscillometry.
   - C. Methacholine challenge test.
   - D. Response to bronchodilators on pulmonary function testing.
   - E. Skin testing.

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5. An 8-year-old girl is being evaluated by her primary care physician with pulmonary function testing before and after bronchodilator administration for a suspected diagnosis of asthma. Which of the following parameters is most important in the diagnosis and evaluation of asthma?
   - A. Closing capacity.
   - B. Ratio of closing capacity to residual volume.
   - C. Ratio of forced expiratory volume in 1 second to forced vital capacity.
   - D. Residual volume.
   - E. Total lung capacity.

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Bronchiolitis

Alyssa H. Silver, MD,* Joanne M. Nazif, MD*

**Department of Pediatrics, Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY*

Practice Gaps

1. Clinicians should be able to identify and diagnose patients with a clinical presentation of bronchiolitis, limiting the use of extensive diagnostic testing.
2. Although bronchiolitis is a condition commonly encountered in pediatrics, there is no single effective therapeutic agent; therefore, with an aim to provide high-value and high-quality care, clinicians should be aware that the main treatment plan for bronchiolitis is supportive care.

Objectives

After completing this article, readers should be able to:

1. Evaluate and diagnose patients with bronchiolitis.
2. Summarize the 2014 American Academy of Pediatrics guidelines for the management and prevention of bronchiolitis.
3. Identify potential current therapies as well as interventions not recommended for routine use in bronchiolitis.
4. Discuss prevention measures for bronchiolitis.
5. Describe the prognosis for patients diagnosed as having bronchiolitis.

INTRODUCTION

Acute bronchiolitis refers to airway inflammation and obstruction of the lower respiratory tract and is caused almost exclusively by viral infection in children younger than 2 years. Commonly, symptoms of bronchiolitis begin with rhinitis or congestion and cough and may develop into symptoms of increasing respiratory distress (tachypnea, wheezing, and accessory muscle use). (1) Severity of bronchiolitis can vary from mild symptoms that can be managed at home to acute respiratory failure requiring invasive ventilation. There is wide variation in care for infants admitted to the hospital with bronchiolitis, which persists despite the existence of guidelines. (2)(3)(4) In 2014, the American Academy of Pediatrics (AAP) published the "Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis" (1) (summarized in Table 1), an updated, revised version of a previous 2006 AAP guideline. (5) The strength of these recommendations are explained in Table 2. (1) Pediatricians should be familiar with these guidelines as well as evidence behind available diagnostic and treatment modalities. Greater

AUTHOR DISCLOSURE Drs Silver and Nazif have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
LOS	length of stay
RSV	respiratory syncytial virus

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TABLE 1. **Summary of the American Academy of Pediatrics Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis**

KEY ACTION STATEMENT	STATEMENT	RECOMMENDATION STRENGTH	LEVEL OF EVIDENCE QUALITY[a]
1a	Clinicians should diagnose bronchiolitis and assess disease severity on the basis of history and physical examination findings	Strong	B
1b	Clinicians should assess risk factors for severe disease, such as age <12 wk, a history of prematurity, underlying cardiopulmonary disease, or immunodeficiency when making decisions about evaluation and management of children with bronchiolitis	Moderate	B
1c	When clinicians diagnose bronchiolitis on the basis of history and physical examination findings, radiographic or laboratory studies should not be obtained routinely	Strong	B
2	Clinicians should not administer albuterol (or salbutamol) to infants and children with a diagnosis of bronchiolitis	Strong	B
3	Clinicians should not administer epinephrine to infants and children with a diagnosis of bronchiolitis	Strong	B
4a	Nebulized hypertonic saline should not be administered to infants with a diagnosis of bronchiolitis in the emergency department	Moderate	B
4b	Clinicians may administer nebulized hypertonic saline to infants and children hospitalized for bronchiolitis	Weak (based on randomized controlled trials with inconsistent findings)	B
5	Clinicians should not administer systemic corticosteroids to infants with a diagnosis of bronchiolitis in any setting	Strong	A
6a	Clinicians may choose not to administer supplemental oxygen if the oxyhemoglobin saturation exceeds 90% in infants and children with a diagnosis of bronchiolitis	Weak (based on low-level evidence and reasoning from first principles)	D
6b	Clinicians may choose not to use continuous pulse oximetry for infants and children with a diagnosis of bronchiolitis	Weak (based on lower-level evidence)	C
7	Clinicians should not use chest physiotherapy for infants and children with a diagnosis of bronchiolitis	Moderate	B
8	Clinicians should not administer antibacterial medications to infants and children with a diagnosis of bronchiolitis unless there is a concomitant bacterial infection, or a strong suspicion of one	Strong	B
9	Clinicians should administer nasogastric or intravenous fluids for infants with a diagnosis of bronchiolitis who cannot maintain hydration orally	Strong	X
10a	Clinicians should not administer palivizumab to otherwise healthy infants with a gestational age of 29 weeks, 0 days or greater	Strong	B
10b	Clinicians should administer palivizumab during the first year of life to infants with hemodynamically significant heart disease or chronic lung disease of prematurity defined as preterm infants on >21% oxygen for at least the first 28 days of age	Moderate	B
10c	Clinicians should administer a maximum of 5 monthly doses (15 mg/kg per dose) of palivizumab during the respiratory syncytial virus season to infants who qualify for palivizumab in the first year of life	Moderate	B
11a	All people should disinfect hands before and after direct contact with patients, after contact with inanimate objects in the direct vicinity of the patient, and after removing gloves	Strong	B
11b	All people should use alcohol-based rubs for hand decontamination when caring for children with bronchiolitis. When alcohol-based rubs are not available, individuals should wash their hands with soap and water	Strong	B

Continued

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TABLE 1. (Continued)

KEY ACTION STATEMENT	STATEMENT	RECOMMENDATION STRENGTH	LEVEL OF EVIDENCE QUALITY[a]
12a	Clinicians should inquire about the exposure of the infant or child to tobacco smoke when assessing infants and children for bronchiolitis	Moderate	C
12b	Clinicians should counsel caregivers about exposing the infant or child to environmental tobacco smoke and about smoking cessation when assessing a child for bronchiolitis	Strong	B
13	Clinicians should encourage exclusive breastfeeding for ≥6 mo to decrease the morbidity of respiratory infections	Moderate	B
14	Clinicians and nurses should educate personnel and family members on evidence-based diagnosis, treatment, and prevention of bronchiolitis	Moderate	C

[a] *Level A = Intervention: Well-designed and conducted trials, meta-analyses on applicable populations. Diagnosis: Independent gold standard studies of applicable populations. Level B = Trials or diagnostic studies with minor limitations; consistent findings from multiple observed studies. Level C = Single or few observational studies or multiple studies with inconsistent findings or major limitations. Level D = Expert opinion, case reports, reasoning from first principles. Level X = Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit or harm.*

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adherence to clinical practice guidelines can help to minimize unwanted variation in care (such as varying rates of albuterol use), which can have unintended consequences (such as the adverse effects of tachycardia and jitteriness or increased length of stay [LOS]), and can help to improve high-value, high-quality care, with improvement in clinically important outcomes for patients. (3)(6)

EPIDEMIOLOGY

As the leading reason for hospitalization in the first year of life, bronchiolitis is responsible for approximately 100,000 hospital admissions annually in the United States. Although the number of admissions declined from 2000 to 2009, the number of emergency department visits, disease severity, use of noninvasive or invasive mechanical ventilation, and hospital charges all increased during this time. Nationwide, hospital charges for patients with bronchiolitis exceeded $1.7 billion in 2009. (7)

Use of molecular detection techniques has made it possible to identify a variety of causative viral agents for bronchiolitis. Respiratory syncytial virus (RSV) is by far the most commonly identified virus, detected in up to 80% of patients, followed by human rhinovirus. Clinical features of bronchiolitis caused by individual viruses are generally similar, although each virus demonstrates slight variation in seasonality and geographic distribution, and there are some data to suggest that RSV may be associated with a more severe illness course. (8) Some studies also point to greater disease severity in infants with co-infection by 2 or more viruses, although data are conflicting. (9) In the United States, RSV bronchiolitis accounts for fewer than 100 deaths annually, although mortality due to bronchiolitis is significantly higher in resource-limited countries. (9)

The epidemiology of RSV differs globally based on meteorologic conditions. In temperate climates, illness from RSV occurs in epidemics based on colder temperatures. In the Northern Hemisphere, infection rates increase from late October through April and peak in January or February. (8) This is followed by wintertime epidemics in the Southern Hemisphere from May to September. (10) During these peak times, viral transmission and disease severity are thought to be facilitated by indoor crowding, the impairment of ciliary function by cold air, and the temperature dependence of innate antiviral immune responses. (8) Alternatively, in tropical or semitropical climates, RSV outbreaks tend to be more common during the rainy season. (10)

PATHOGENESIS

The pathogenesis of bronchiolitis involves a combination of airway edema, increased mucus production, and necrosis of airway epithelial cells due to direct cytotoxic injury. (8) RSV transmission occurs from person to person either by direct inoculation of nasal mucosa with contaminated secretions or by inhalation of large infectious droplets. Virus replicates in the nasal epithelium, and an exaggerated immune response occurs, with an influx of natural killer cells, lymphocytes, and granulocytes into the epithelium. After an incubation period of 4 to 6 days from transmission, upper respiratory tract symptoms appear, including nasal congestion and rhinorrhea. (9)

In approximately one-third of infected patients, infection then spreads to the lower respiratory tract by sloughing and

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aspiration of necrotic nasopharyngeal epithelial cells. (9) Viral replication subsequently occurs in the mucosal epithelial cells of the bronchioles. Similar to the upper respiratory tract, the resultant immune response in the lower tract leads to edema, further sloughing of epithelial cells, and mucus secretion. This leads to airway narrowing and obstruction, further worsened by impaired ciliary function. Cough, wheezing, tachypnea, nasal flaring, and retractions are the clinical manifestations of the airway obstruction. Distal air trapping causes hyperinflation and localized atelectasis. Mismatching of ventilation and perfusion leads to further increased work of breathing and hypoxemia. Fever is not universal, occurring in approximately 50% of patients. An uncomplicated illness may last 1 to 3 weeks before all symptoms are completely resolved, although viral shedding may last up to 4 weeks, especially in very young or immunocompromised patients. Unfortunately, despite the robust immune response, RSV infections occur throughout life, even in the absence of detectable antigenic change. (9)

RISK FACTORS

For most previously well infants, bronchiolitis is generally a self-limited disease. However, a subset of patients may be at risk for more severe disease, with several host and environmental factors contributing to severity risk. Age is the most important predictor of disease severity, with greatest risk between 1 and 3 months, when protective maternal antibodies wane. (9) Similarly, preterm infants, especially those less than 29 weeks of gestation who miss the window of greatest transplacental transfer of antibodies, are at higher risk for severe disease. Other severity risk factors include chronic lung disease of prematurity and hemodynamically significant congenital heart disease, especially in patients with pulmonary hypertension or congestive heart failure. Trisomy 21, lower weight, and neuromuscular disorders have also been described as independent predictors of severe bronchiolitis. (11) Sex may also play a role, with boys seeming to be at higher risk for severe illness than girls. There does not seem to be a disparity in rate of hospitalization between African American and white infants; data for other racial and ethnic groups are limited. (9)

Several recent studies have focused on preventable environmental risk factors for severe bronchiolitis. Although the mechanism is not completely understood, cigarette smoke has been shown to affect the incidence and severity of bronchiolitis. Infants with in utero tobacco smoke exposure were more likely to be admitted to the ICU for bronchiolitis in one study, (12) and in another, postnatal tobacco smoke exposure was associated with significantly increased odds of developing severe disease. (13) Other research suggests that air pollution, even at levels widely accepted as "safe," may increase bronchiolitis risk. (14)

CLINICAL ASPECTS

The diagnosis of bronchiolitis is made primarily based on history and physical examination findings. AAP guidelines recommend against the routine use of laboratory or radiographic testing. Patients often present with a history of a few days of initial upper respiratory symptoms (rhinorrhea, congestion) and fever, progressing into lower respiratory tract symptoms. Prominent lower respiratory tract symptoms include cough, wheezing, tachypnea, and signs of

TABLE 2. **Guideline Definitions for Evidence-Based Statements**

STATEMENT	DEFINITION	IMPLICATION
Strong recommendation	A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), and quality of evidence is excellent or unobtainable.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Moderate recommendation	A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), and the quality of evidence is good but not excellent (or is unobtainable).	Clinicians would be prudent to follow a moderate recommendation but should remain alert to new information and sensitive to patient preferences.
Weak recommendation (based on low-quality evidence)	A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), but the quality of evidence is weak.	Clinicians would be prudent to follow a weak recommendation but should remain alert to new information and very sensitive to patient preferences.
Weak recommendation (based on balance of benefits and harms)	Weak recommendation is provided when the aggregate database shows evidence of both benefit and harm that seem similar in magnitude for any available courses of action.	Clinicians should consider the options in their decision making, but patient preference may have a substantial role.

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increased work of breathing (intercostal, subcostal, or supraclavicular retractions; nasal flaring; head bobbing; or grunting). (9) Apnea alone may also be an initial presentation of bronchiolitis, particularly in infants younger than 2 months. Risk of apnea in young infants varies in studies from less than 1% to 24%. (9)(15) Infants can present with difficulty feeding and dehydration due to upper respiratory tract obstruction from mucus production and airway edema.

Physical examination findings vary from mild, with tachypnea, to severe, with complete respiratory failure. Vital sign changes include tachypnea, hypoxemia, and tachycardia (due to dehydration or as a reflection of hypoxemia). (16) Other physical findings include varying measures of increased work of breathing, including varying degrees of retractions, head bobbing, nasal flaring, and grunting. Signs of dehydration may also be seen on examination, including delayed capillary refill, sunken fontanelle, dry mucous membranes, and poor skin turgor. Findings on auscultation can include diffuse wheezing, crackles, coarse prolonged expiratory phase, and transmitted upper airway sounds.

The course of illness can be varied and dynamic, changing from moment to moment. The typical course of illness peaks at approximately day 3 to 4 of illness (16); however, this can have significant variation. Similarly, in assessing patients with bronchiolitis, physical examination findings may vary from moment to moment so that often-repeated observations are helpful to truly assess clinical severity. The nature of inherent variability in children with bronchiolitis has made it difficult for a single clinical severity scoring system to be widely accepted in predicting severity or clinical disposition. (17)

The AAP clinical practice guideline specifically recommends against the routine use of chest radiography for the evaluation of bronchiolitis. (1) Most patients with bronchiolitis have chest radiographs with hyperinflation, possibly with atelectasis or infiltrates, which often do not correlate with disease severity or aid with management. (18) Abnormal findings may lead to increased use of antibiotics without true underlying bacterial pneumonia, increasing both potential harms to the patient and health-care costs. (19)(20) Similarly, the AAP clinical practice guideline recommends against routine viral testing given that identification of a given virus does not alter management. (1) The only circumstance for which it could be considered is in the setting of suspected potential influenza infection if the clinical presentation as well as current community epidemiologic factors support the possibility of influenza infection, and, therefore, influenza antiviral agents could be considered. (16)

MANAGEMENT

The management of bronchiolitis is largely supportive; despite numerous trials of various medical therapeutic interventions, no clear single therapy has been found to be significantly beneficial. The mainstay of therapy begins with an assessment of need for supportive care by assessing hydration status and oxygenation. Dehydration can occur due to increased insensible losses with tachypnea, fever, and increased secretions or due to decreased oral intake in the setting of decreased energy, increased work of breathing, or congestion impeding oral intake. Support for dehydration can be provided in the form of encouraging frequent small aliquots of oral, nasogastric, or intravenous hydration, without a single modality being superior to the others. Severe bronchiolitis may be associated with greater potential for hyponatremia, (21) and management with hypotonic fluids may also be associated with less favorable outcomes. (22)

Hypoxemia may also accompany bronchiolitis, and it may be intermittent or variable due to the intermittent nature of plugging of bronchioles by mucus resulting in ventilation-perfusion mismatch. Whereas in the past there has been debate about acceptable levels of oxygen saturation, the most recent AAP clinical practice guideline suggests that clinicians may choose to not give supplemental oxygen therapy if saturations are greater than 90%. (1) Similarly, for children hospitalized with bronchiolitis, clinicians may choose not to use continuous pulse oximetry for those who do not require supplemental oxygen. Both of these recommendations have been shown to be safe compared with previous oxygen targets and pulse oximetry measurement practices. (23)(24) The use of continuous pulse oximetry is not only potentially associated with increased LOS but also occasionally feeds into the plight of overdiagnosis due to frequent false alarms, which can additionally lead to subsequent decreased rest for patients and families. (25)(26)

Although a common measure of supportive care, there is currently insufficient evidence to recommend for or against nasal suctioning as a potential intervention to help with upper airway obstruction due to mucus production. However, there is evidence to recommend against deep suctioning because it can prolong LOS in infants hospitalized with bronchiolitis. (27) Possible explanations for this finding are that deep suctioning may cause more airway trauma and, therefore, edema and irritation, inadvertently prolonging symptoms, or, alternatively, that the use of a larger-caliber catheter for nasopharyngeal suctioning may be more effective in clearing nasal secretions and, thus, improve symptoms sooner. (27) Similarly, chest physiotherapy has been examined as a potential supportive measure that overall has

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been shown to be ineffective at improving outcomes such as LOS or disease severity; however, there are some conflicting more recent studies that may suggest benefit, specifically using passive expiratory techniques, such as providing bimanual thoracic and abdominal pressure during expiration and holding the pressure for a few respiratory cycles. (28)(29) There is some potentially conflicting evidence on this topic due to the heterogeneity of studies in the sense that the severity of illness in patients included in these studies varies, as well as the chest physiotherapy techniques vary between studies. (29) However, currently there is not enough benefit shown in any particular group or method to warrant general recommendation.

Various studies and systematic reviews (30)(31)(32) have demonstrated that neither albuterol nor any other β-agonist bronchodilators should be used to treat children with bronchiolitis, concluding that the adverse effects and costs supersede possible benefits. (1) Similarly, racemic epinephrine and other α receptor agonists should not be used to treat bronchiolitis. (33) One study's findings conflict with this statement; the study showed some potential benefit when combining racemic epinephrine with corticosteroids specifically in the emergency department setting. (34) However, this has not been conclusively determined. Similarly, corticosteroids have been shown to be ineffective in the routine treatment of bronchiolitis. (35)

Nebulized hypertonic saline is a treatment option that has received recent attention due to conflicting clinical trial results, the conflict coming from reported widely varying LOSs, particularly in studies conducted outside the United States; but even when solely examining studies conducted in the United States, differences exist. (36)(37)(38) Several meta-analyses and systematic reviews have also come to different conclusions. (39)(40)(41)(42) The most recent publication using a more novel method, trial sequence analysis, has concluded that results from previous meta-analyses that show a benefit likely represent a type I error (concluding that a statistically significant treatment exists, when one does not exist in reality). Therefore, clear benefit from hypertonic saline cannot be concluded. (43)

Heated humidified high-flow nasal cannula oxygen is a treatment modality that has more recently gained popularity in use for the treatment of infants with bronchiolitis, although its efficacy has not been conclusively proved. There are data to suggest that heated humidified high-flow nasal cannula oxygen may decrease respiratory effort and work of breathing, as well as some potential evidence of decreasing need for escalation of care; however, again, conflicting data exist. (44)(45)(46) All of these studies, as well as additional studies focusing on potential safety issues, including feeding while on high-flow nasal cannula, suggest that heated humidified high-flow nasal cannula oxygen therapy is a safe treatment modality. (47)

Antibiotic drug therapy is not recommended for the treatment of bronchiolitis unless an identified concomitant bacterial infection (such as acute otitis media or urinary tract infection) is confirmed or suspected. Studies vary on the potential risk of serious bacterial infection in infants with bronchiolitis, which also differs by the age of the patient in question. Although bacteremia and meningitis are extremely rare, infections such as urinary tract infection or acute otitis media may be more common. (48)(49) Laboratory testing to confirm concomitant bacterial infection when suspected should be obtained before initiating antibiotic drug use. Antiviral drug therapy is not recommended unless specifically in the setting of influenza infection, as noted previously herein. (16)

Measures to prevent bronchiolitis are important for the pediatric provider to be familiar with to assist in treating patients and educating families and caregivers. (1) Premature infants or infants with comorbidities (such as hemodynamically significant heart disease, immunodeficiency, or neuromuscular disease) should receive prophylaxis with palivizumab as appropriate during the RSV season, as per AAP guidelines, which may vary year to year as to eligibility and specific recommendations, with the most recent recommendations referenced. (50) In the clinical setting, appropriate isolation precaution measures should be used to minimize spread of infection to other patients or caregivers. When speaking with families and caregivers of young infants and children, clinicians should also emphasize measures that will decrease risk of developing or spreading bronchiolitis, such as appropriate hand hygiene (using alcohol-based hand rubs or, when not available, soap and water) and decreasing exposure of young infants in particular to others who are ill. Other measures that may decrease both the occurrence and severity of bronchiolitis are decreasing tobacco smoke exposure as well as encouraging breastfeeding.

When specifically discussing emergency department or inpatient management of bronchiolitis, differences in care practices have been shown to correlate with differences in hospital costs and LOS. Overuse of resources that are not supported by the AAP guidelines has been associated with increased LOS without the benefit of decreased readmission. (3) Clinical pathways that reinforce the conservative approach (eg, not using bronchodilators) have been associated with decreased LOS, (51) decreased use of ineffective therapies (such as bronchodilators or corticosteroids), and decreased LOS without affecting readmissions. (52)

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The existence of the AAP clinical practice guideline has allowed for significant opportunity to implement various quality improvement initiatives, such as using clinical pathways at an institution level, and to implement initiatives that have resulted from national collaboratives. (53)(54)(55)(56) Potential initiatives could target various outcomes (such as LOS) or reduce evaluation or treatment measures that are not routinely recommended (such as chest radiography or bronchodilators, respectively).

PROGNOSIS

By nature, bronchiolitis is a self-limited disease with a relatively good prognosis. Mortality risk is relatively low and declining in otherwise healthy children, including those younger than 1 year, with recent analysis revealing an odds ratio of 0.25 in the United States when examining in-hospital mortality out of all patients hospitalized with bronchiolitis, comparing 2009 and 2000 mortality data, which approximates fewer than 100 deaths annually. (7)(9) The most common sequela attributed to bronchiolitis is the development of reactive airway disease or asthma later in childhood. Although the reported risk varies from 20% to 60%, infants with severe bronchiolitis, such as those requiring hospitalization (particularly infants <6 months of age), have a higher risk of developing asthma later in life. (57)(58) Asthma may occur with increased frequency in infants with a personal or family history of atopy. Therefore, counseling to all families after the initial episode of bronchiolitis should include advice to be attentive to the potential for wheezing or increased respiratory distress if the child develops another viral respiratory illness in the future.

Summary

- Specific evidence is summarized in Table 1.
- Based on strong research evidence, bronchiolitis is a clinical diagnosis and, therefore, clinicians should not routinely use chest radiography or laboratory tests to evaluate. (1)
- Based on some research as well as consensus, (1) clinicians may choose not to use continuous pulse oximetry to monitor hospitalized patients with bronchiolitis and may choose to provide only supplemental oxygen therapy for oxygen saturations less than 90%. (23)(24)
- Based on strong research evidence, treatment of bronchiolitis should not routinely include the use of bronchodilators, corticosteroids, or antibiotics. (1)(31)(32) Although there has been early conflicting evidence on the utility of nebulized hypertonic saline, more recent analyses, particularly in US populations, lean toward recommending against its use for routine treatment of bronchiolitis. (40)(43)
- Based on strong research evidence, as well as some consensus, clinicians should educate and counsel families about bronchiolitis and ways to minimize risk, including proper hand hygiene, decreasing tobacco smoke exposure, and encouraging breastfeeding. (1)
- Strong research evidence supports that clinicians should use palivizumab prophylaxis in specific populations based on specific annual recommendations. (50)
- Based on some research evidence, clinicians could consider using clinical pathways incorporating American Academy of Pediatrics clinical practice guidelines to help minimize variation of care, improve outcomes for patients, and prevent overuse of therapies not routinely recommended. (53)(54)(55)(56)
- Overall prognosis for infants and children with bronchiolitis is good because it is a self-limited illness. (1) Based on some research evidence and consensus, given the association with potential for future risk of wheezing and development of asthma, providers and caregivers should remain vigilant for future signs and symptoms consistent with asthma. (57)(58)

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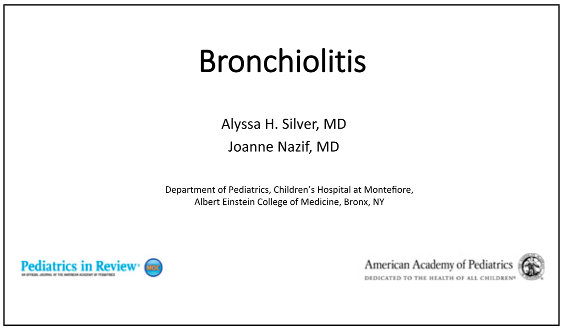

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Alyssa H. Silver, MD
Joanne Nazif, MD

Department of Pediatrics, Children's Hospital at Montefiore,
Albert Einstein College of Medicine, Bronx, NY

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1. A previously healthy 2-month-old boy presents to the clinic with a 12-hour history of "breathing fast," rhinorrhea, congestion, and cough. He has been breastfeeding normally until this morning, when he was noted to stop latching on due to congestion and cough. The baby was born at 38 weeks' gestation but was small for gestational age due to placental insufficiency. The mother had an uneventful pregnancy. She smoked in the first trimester but stopped smoking when she learned she was pregnant. Family history is significant for asthma. The baby is diagnosed as having bronchiolitis. You explain to the family that because it is early in the course of the disease, the clinical course could potentially worsen. Which of the following is the most important predictor of disease severity in this patient?
   A. Age.
   B. Being born small for gestational age.
   C. Breastfeeding.
   D. Family history of asthma.
   E. Male sex.
2. Physical examination of the patient in the vignette in question 1 shows a temperature of 100.4°F (38.0°C), respiratory rate of 50 breaths/min, heart rate of 140 beats/min, and oxygen saturation of 95% on room air. On physical examination the baby is alert and awake but in mild respiratory distress with subcostal retractions. There is no head bobbing but there is nasal flaring and nasal congestion. On lung auscultation, mild end expiratory wheezing is diffusely heard. He has moist mucous membranes, and his cardiac examination findings are normal. The rest of the examination findings are normal. In evaluating the respiratory illness in this patient, which of the following is the most useful method in making the diagnosis of bronchiolitis?
   A. Acute and convalescent serum specimens.
   B. Chest radiography.
   C. Complete blood cell count.
   D. History and physical examination.
   E. Nasopharyngeal swab for viral culture.
3. A 4-month-old infant presents to the emergency department (ED) in respiratory distress in January. She was born at 36 weeks' gestation without complications. She does attend child care, where there are multiple other children with "colds." Her mother reports that the baby has had 2 days of increasing difficulty breathing, with nasal congestion, rhinorrhea, and low-grade fever. This morning the mother noted significant work of breathing, with nasal flaring and retractions, and brought the baby to the ED. On physical examination the baby has a temperature of 99.7°F (37.6°C), respiratory rate of 65 breaths/min, heart rate of 180 beats/min, and oxygen saturation of 88% on room air. Blood pressure is within normal values. The infant appears well-developed, but she is in moderate respiratory distress. There is thick nasal discharge. On examination some head bobbing and occasional grunting are noted. On auscultation there are diffuse wheezes and a prolonged expiratory phase. A diagnosis of viral bronchiolitis is made. In addition to deep nasal suctioning, which of the following is the next best step in management in this patient?
   A. Administer a nebulized albuterol treatment.
   B. Begin supplemental oxygen.
   C. Obtain a chest radiograph.
   D. Order a complete blood cell count and a blood culture.
   E. Start empirical broad spectrum antibiotics.

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4. A 6-month-old boy is brought to the clinic by his parents for follow-up after discharge from the hospital where he was admitted for 72 hours for respiratory syncytial virus (RSV) bronchiolitis. The parents are very concerned about their 2 older children in the home getting sick and ask how they might best prevent the spread of the illness. Which of the following is the most effective measure to decrease the risk of RSV transmission?
    A. Administer palivizumab to the 6-month-old.
    B. Begin prophylactic antibiotics for the other children.
    C. Emphasize appropriate hand hygiene.
    D. Ensure that all household members are up-to-date with recommended vaccines.
    E. Keep the older children home from school for 7 days.
5. The parents of the infant described in the vignette in question 4 are concerned whether this RSV episode would result in late and long-term sequelae. They seek information from the clinician during this visit. The clinician reassures the parents that the overall prognosis for infants and children with bronchiolitis is good with minimal later sequelae in low-risk patients. In explaining the potential long-term sequelae reported in children after bronchiolitis episodes, the clinician will most likely mention which of the following as a common sequela attributed to bronchiolitis?
    A. Chronic obstructive pulmonary disease.
    B. Epilepsy.
    C. Reactive airway disease.
    D. Recurrent pneumonia.
    E. Sinusitis.

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Bronchiolitis

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Acne Vulgaris in the Pediatric Patient

Rosalind Ashton, MD, MSc,* Miriam Weinstein, MD, FRCPC†

*King's College London School of Medical Education, St. John's Institute of Dermatology, London, United Kingdom

†The Hospital for Sick Children, Toronto, Ontario, Canada

Practice Gap

Acne vulgaris is a common disease seen in pediatric practices, and pediatricians should be able to develop management strategies using standard therapies, including retinoids.

Objectives

After completing this article, readers should be able to:

1. Describe the pathophysiology of acne.
2. Outline treatment options based on a patient's clinical presentation.
3. Discuss mechanisms of action and adverse effects of common acne medications.
4. Explain treatment options for postacne sequelae.

INTRODUCTION

Acne vulgaris is a ubiquitous disease of the pilosebaceous unit, characterized by a long-term course with recurrences and relapses. It affects approximately 85% of adolescents and may persist until well into a patient's 20s and 30s. (1)(2)(3) Psychological sequelae can be substantial and should not be underestimated. This common, very visible skin condition presents at a time when appearance is acutely important and noticeable disease marring that appearance is distressing. Embarrassment contributes to lower self-esteem and feelings of unattractiveness and worthlessness, which may be present not only during active flare-ups but also with long-lasting postinflammatory hyperpigmentation and permanent scarring. (4)

The aim of this review is to offer up-to-date information on pathophysiology, evaluation, and management strategies for this common disease.

The treatment of acne conglobata, acne fulminans, cloracne, drug-induced acne, hidradenitis suppurativa, inflammatory disorders in which acne is a major feature, acne keloidalis nuchae, and dissecting cellulitis of the scalp is beyond the scope of this review but should be maintained in the differential diagnosis when clinically relevant.

TYPES OF ACNE

Although the bulk of this article focuses on acne in adolescence, mention of acne during earlier childhood is addressed first.

AUTHOR DISCLOSURE Dr Ashton has disclosed no financial relationships relevant to this article. Dr Weinstein has disclosed funding from La Roche Posay through her hospital's charitable foundation for a program to teach patients with eczema and their families about the disease and how to manage it; is an advisory board leader/lecturer on eczema for Pfizer; is an advisory board member for Amgen and Pfizer on eczema; is an advisory board consultant for Sanofi Genzyme; is a consultant for Unilever; and is a consultant for Paladin Labs. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

BPO	benzoyl peroxide
D+A/BPO	doxycycline + adapalene/benzoyl peroxide
DRESS	drug reaction with eosinophilia and systemic symptoms
FDA	Food and Drug Administration
IBD	inflammatory bowel disease
PDL	pulsed dye laser
TLR	Toll-like receptor

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Neonatal Acne (Neonatal Cephalic Pustulosis)

Having its onset in the first 2 weeks of life and defined as presenting at less than 6 weeks of age, neonatal acne is characterized by papules and pustules usually on the face. It is believed that this eruption is not a true acne but rather an inflammatory reaction to *Malassezia* species such as *Malassezia furfur* (5) and *Malassezia sympodialis,* (6) and it is best referred to as *cephalic pustulosis*. However, there is some controversy about whether this acneiform eruption is related to *Malassezia* species. Increased sebum production, likely due to circulating maternal androgens, by active sebaceous glands during this period also contributes. This eruption typically self-resolves but may be treated with topical 2% ketoconazole twice daily, further supporting the argument for a relationship with *Malassezia*. Often a mild topical corticosteroid is added for its anti-inflammatory benefit.

Infantile Acne

The age ranges used to define the following categories refer to the age at onset of disease rather than the age at which the patient presents to a health-care provider. Acne occurring between 6 weeks and 1 year of age defines infantile acne. It is more common in males, typically presenting as inflammatory papules on the cheeks, although true comedones can be present. This may last for 6 to 12 months or for several years. (7) It is considered more difficult and important to treat because scarring is significantly more likely to occur. Most cases of infantile acne resolve by age 4 years, but there is weak evidence that it is a predictor of more severe acne as an adolescent. (8) Patients, especially older infants, with other signs of hormonal abnormalities (eg, virilization) warrant evaluation and referral to a pediatric endocrinologist because this may be the first sign of a treatable endocrinopathy. Treatments, although all off-label, are the ones used for adolescent acne, including oral therapy where necessary.

Mid-childhood Acne

Defined as presenting between 1 and 7 years of age, mid-childhood acne is very rare and should raise suspicion for an endocrinopathy. Appropriate evaluation includes looking for causes of hyperandrogenism, including Cushing disease, virilizing tumors, and congenital adrenal hyperplasia. History and physical examination, family history, analysis of height and weight charts, and serologic testing for total and free testosterone, dehydroepiandrosterone, 17-hydroxyprogesterone, and luteinizing hormone/follicle-stimulating hormone should be performed. (9) Treatment should address the underlying cause of acne, which should be managed concurrently by a pediatric endocrinologist. The dermatologic options are much the same as for adolescent acne.

Preadolescent Acne

Acne occurring between 7 and 11 years of age is less common and may require evaluation and possible referral to a pediatric endocrinologist. (10) Although acne in this age group is usually due to isolated premature adrenarche, it may be the first presenting sign in a child with true precocious puberty, congenital adrenal hyperplasia, polycystic ovarian syndrome, or a rare virilizing tumor. Adenoma sebaceum (facial angiofibromas), a key feature of tuberous sclerosis, usually appears before age 10 years and can mimic facial acne. (11) Acne caused by an endocrinopathy will always have other presenting signs on physical examination, including body odor, advanced height and weight, breast development, and axillary and pubic hair. A thorough history and physical examination should be performed when a patient presents with acne in this age group. Treatment, in addition to addressing the underlying cause, is largely the same as for adolescent acne (except for tetracycline antibiotics).

PATHOPHYSIOLOGY

The hallmark of acne is microcomedones, which evolve into the noninflammatory lesions of open and closed comedones (colloquially known as *blackheads* and *whiteheads*). Comedones are usually the first lesions to occur. Inflammatory lesions manifest as papules and pustules, occasionally developing into nodules, a sign of severe disease. All lesions may be present in combination and in varying stages of healing or development. Scarring has many descriptive morphologies: atrophic, icepick, boxcar, and rolling. (12) Keloid scarring may also occur. Distribution predominantly affects areas where there is an increased density of pilosebaceous units, such as the face (usually first appearing along the "T-zone" distribution of the brow, glabella, and bridge of the nose), chest, shoulders, and back. Development of acne is correlated with onset of adrenarche rather than with chronologic age.

A tetrad of inflammation, abnormal shedding of keratinocytes, increased production of sebum, and association with *Proprionibacterium acnes* contributes to the pathogenesis of acne. (13)

Increased production of sebum by the sebaceous glands is associated with increased androgenic activity by the adrenals and gonads, occurring during puberty. A

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sebum-rich environment alters desquamation, contributes to follicular plugging, and encourages growth of *P acnes.* (13)

P acnes, a gram-positive bacillus, contributes to acne lesions by accumulating in a plugged follicle and releasing extracellular debris, of which many components are immunogenic and promote inflammation, including heat shock proteins, porphyrin, protease, and squalene peroxides. (13) This release not only attracts immune cells such as neutrophils, monocytes, and lymphocytes, causing a local inflammatory response, but also contributes to a cascade of proinflammatory events inside the distended follicle, ultimately causing rupture and spilling of bacterial contents and cytokines into the dermis. This results in papules, pustules, and nodules. *P acnes* is also able to create a biofilm, a process that bacteria use to become more adherent to a surface. (14) This biofilm is more prevalent in individuals with acne, and it may act as a barrier to antibiotic penetration. (15)

Toll-like receptors (TLRs) are part of the innate immune system and are responsible for recruiting pro-inflammatory cells when threatened by pathogens. There is a positive correlation between the severity of acne lesions and the concentration of cells expressing TLR-2. *P acnes* binds to TLR-2, promoting inflammatory cells to make their way into the pilosebaceous unit to lyse the bacterial invader. It is not surprising, then, that combination therapies such as benzoyl peroxide (BPO), which is bactericidal against *P acnes,* and a topical retinoid, which helps downregulate TLR-2, thereby decreasing inflammation, have been shown to be efficacious. (16)

Acne treatments are, therefore, focused on targeting 1 or more components of this pathophysiologic tetrad.

ACNE AND HYGIENE

Facial cleansing is a common part of many patients' skin care routine and acne management. Data are lacking to strongly support the role of cleansing as an important therapeutic intervention. However, cleansing is reasonable and may remove excess sebum and debris, which many patients prefer. It is important to counsel patients that washing does not need to be done multiple times a day; overzealous washing with harsh or abrasive products may irritate skin or strip it of its moisture, disturbing the barrier function of the stratum corneum and encouraging more sebum production. (17)(18) Explaining that acne is not infectious or a result of lack of cleanliness may also be useful when explaining the roles of gentle cleansing and application of medication.

ACNE AND DIET

We know that the Western diet (often described as a high glycemic index diet) upregulates insulin/insulinlike growth factor 1. (19) This point, compounded with the fact that there is already an upregulation of insulinlike growth factor 1 during puberty, exaggerates sebaceous gland cell proliferation and contributes to increased sebum production in this already upregulated time of development. (20) Randomized prospective trials on this topic are lacking, although a small older randomized trial that looked at 43 male patients with acne noticed improvement in their skin as well as BMI after a 12-week low glycemic index diet. (21)

In 2016, LaRosa et al (22) conducted a case-control study looking at 225 adolescents with moderate acne (as reported by a dermatologist using the Global Acne Assessment Scale) and those without acne. Using self-reported diet interviews, the authors found that total dairy consumption was slightly higher in the acne group than in the control group, reaching significance, with an association especially between acne and skim milk consumption. (22) Full-fat milk was not associated with higher rates of acne in this study, but the opposite was found in 2,489 high school students, especially in male participants, in a 2017 Norwegian questionnaire-based study. (23) Both sets of authors acknowledged the need for prospective studies showing the impact of dairy elimination in diet before making specific dietary recommendations for patients with acne. We, therefore, recommend a balanced diet as supported by the American Food Guide. (24)

EVALUATION

Several acne severity grading scales exist, including the Global Acne Grading System (Table 1), the Global Acne Assessment Scale, the Leeds scale, and the newly described patient-centered acne severity scale. (25)(26)(27)(28) The first 3 are validated. We encourage the serial grading of lesions using a single consistent scale and the Dermatology Life Quality Index before and during treatment. Consistent use helps to survey the evolution of improvement or to decide whether the clinician needs a new strategy. One should consider clinical photography.

Broadly, mild acne is described as limited disease consisting of noninflammatory comedones and/or minimal inflammatory lesions. Moderate acne usually has more lesions and may have a greater spread. Severe acne usually denotes acne with high risk of scarring and/or scarring and, possibly, nodules (Figs 1-3). (29)(30)

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TABLE 1. **Global Acne Grading System**

LOCATION	FACTOR × GRADE (0-4) = LOCAL SCORE
Forehead	2
Right cheek	2
Left cheek	2
Nose	1
Chin	1
Chest and upper back	3

Global score = summation of local scores: 0, none; 1-18, mild; 19-30, moderate; 31-38, severe; ≥39, very severe. Grades: 0, no lesions; 1, ≥1 comedone; 2, ≥1 papule; 3, ≥1 pustule; 4, ≥1 nodule.

Adapted with permission from Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. Int J Dermatol. 1997;36(6):416–418. © 1997 Blackwell Science Ltd.

MANAGEMENT

Choosing therapy for acne vulgaris can be overwhelming because there are many options and products available both over the counter and by prescription. There is no single best therapy for acne management because many factors need to be considered in selecting therapy. Often trials of different products may be needed to establish the most effective and best-tolerated therapies.

There is not necessarily a common starting point for all patients with the same presentation of acne. Selection of a treatment plan needs to include factors such as the mechanism of action of medication, the extent of acne, the morphology of acne, tolerance of medications, compliance with treatment regimens, cost, and patient preference. The Management section highlights the types and roles of medications, and Table 2 helps the clinician consider which treatments to select for given clinical situations. For example, a patient with mild comedonal acne and oily skin may do well starting with a medium-strength topical retinoid, whereas a patient with similar acne but severe dryness from atopic dermatitis may need to use a very mild retinoid every other night or even try a BPO, which is mostly an anti-inflammatory medication but can have some mild comedolytic activity.

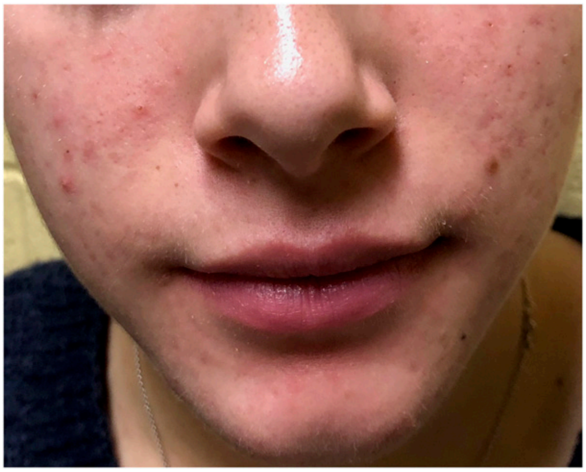

Figure 1. Moderate, mixed inflammatory and comedonal acne.

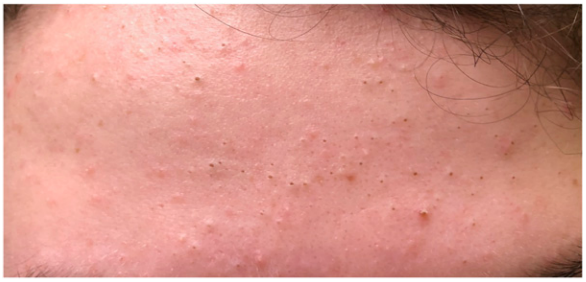

Figure 2. Moderate to severe comedonal acne.

Management should begin with an explanation of acne and management of expectations. Patients and their families should understand that acne is best thought of as a chronic disease of adolescence and that the goal is control, not cure. Therapy should be tailored to the patient and include consideration of the severity and extent of disease, concomitant skin disease such as atopic dermatitis, propensity for scarring, patient reliability/motivation, cost, tolerability of therapy, and degree of health literacy of the patient and the family. A trial of therapy must be given an appropriate amount of time to exert its effects, and patients must be counseled on adverse effects and what to expect to ensure maximum satisfaction and compliance.

In addition to topical and systemic therapies, patients should be counseled on avoidance of comedogenic cosmetics and moisturizers and mechanical friction. Picking at lesions risks scarring and may be a manifestation of an underlying psychiatric condition, especially in young girls,

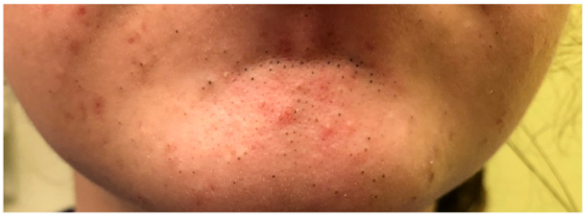

Figure 3. Severe comedonal acne.

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TABLE 2. **Suggested Management Approaches for Select Clinical Situations**

CLINICAL/PATIENT FEATURE	MANAGEMENT STRATEGIES TO CONSIDER
Morphology	
Mostly comedonal	Topical retinoid ± BPO
Mostly inflammatory	Topical antibiotic with BPO or BPO alone
Mixed comedonal/inflammatory	Systemic treatment (oral antibiotic and/or OCP)
	Topical therapy + (oral antibiotic and/or OCP)
	Topical retinoid + topical BPO ± topical or oral antibiotic ± OCP
Severity	
Mild	Topical therapy
Moderate	Topical therapy and/or systemic treatment (oral antibiotic and/or OCP)
Severe	Consider isotretinoin
Extent	
Face	Topical therapy (if not severe); consider fixed-dose combination topical and/or oral therapy
Chest	Topical and/or systemic treatment (oral antibiotic and/or OCP)
Back	If widespread consider oral therapy
Compliance	
Good	Multiple medications applied at separate times may be appropriate
Limited	Consider fixed-dose combination therapy
Expense of medications	
Affordable/covered	Combined/fixed-dose combination products
Unaffordable/noncovered	Products used separately may be less costly but effective
History of eczema or sensitive skin	
Present	May need milder retinoid or less frequent application
Absent	Usually tolerate topical products

BPO=benzoyl peroxide, OCP=oral contraceptive pill.

a compulsive syndrome known as acne excoriée, which can be a component of body dysmorphic disorder. (31) Encouraging sun protection especially when selecting medication with photosensitivity adverse effects is also important.

Mild to Moderate Acne

Topical therapies are recommended as first-line treatment of mild to moderate acne and are also useful adjuncts when hormone therapy or oral antibiotics are used for moderate acne. Topical therapy includes BPO, topical antibiotics, topical retinoids, and topically applied acids. Retinoids are usually included in the regimen when comedones are present and can play a role in maintenance/prevention as well once control is established. Often but not always, moderate acne may require oral therapy with antibiotics or hormone therapy. Adding topical BPO to reduce bacterial resistance and/or a topical retinoid to help with comedones is often warranted.

Severe Acne

Severe nodulocystic disease is an indication for isotretinoin, although other strategies can be used for severe acne and for patients who are unable or unwilling to use isotretinoin for severe acne.

A well-designed randomized, placebo-controlled trial from 2016 looked at combination adapalene 0.3% and BPO 2.5% gel and demonstrated efficacy in moderate to

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severe nonnodulocystic acne with good tolerability. This is the first study of a topical therapy showing excellent results against moderate to severe nonnodulocystic acne with good tolerability and should be considered for patients who refuse isotretinoin therapy. (32)

Oral doxycycline has also been studied in combination with adapalene 0.1%and BPO 2.5% (D+A/BPO) against isotretinoin for severe nodular acne. A 2014 randomized controlled trial concluded that D+A/BPO showed a favorable efficacy and safety profile compared with isotretinoin. D+A/BPO also seemed to reduce inflammatory lesions more rapidly by the second week of treatment. Although isotretinoin demonstrated superior total results after 20 weeks, this combination is an alternative for patients who are unwilling or unable to take isotretinoin and can be offered as an option for treatment of severe nodular acne. (33)

Acids

Salicylic Acid. Salicylic acid, a β-hydroxy acid, is an ingredient in many over-the-counter acne products, including cleansers. It exerts a desquamative effect on the skin, causing keratinocyte discohesion in congested follicles by dissolving lipid bonds, thereby preventing comedones and improving the appearance of current ones. (34)(35) Its exfoliating abilities have made it a popular peeling agent in 20% or greater concentrations for active acne as well as postacne scarring.

Azelaic Acid. Azelaic acid, a naturally occurring dicarboxylic acid, is bactericidal against *P acnes*, is anti-inflammatory, and reduces the proliferation of keratinocytes, thereby decreasing comedone formation. (36) This is a popular product in darker-skinned individuals because it may help to lighten post-inflammatory hyperpigmentation of old lesions via its antiproliferative effects on abnormally proliferating melanocytes and antityrosinase activity. (37) It is available in a 20% cream and a 15% gel and is typically applied twice daily. Adverse effects include mild to moderate irritation at the application site, which usually subsides after 2 to 4 weeks of continued use.

Glycolic Acid. Glycolic acid, an α-hydroxy acid, promotes exfoliation and desquamation of keratinocytes in the corneal layer. It is a widely used superficial and medium peeling agent used in cosmetic practices with evidence of improvement of acne scars. (38)

Anti-Inflammatory

Benzoyl Peroxide. BPO is a common active ingredient in many over-the-counter facial cleansers and anti-acne creams and gels. It is bactericidal against *P acnes*, lysing the cell wall by release of oxygen free radicals, and has comedolytic properties possibly by decreasing accumulation of free fatty acids, thereby enhancing follicular desquamation and decreasing follicular plugging. It has a fast onset of action and should be considered for initial treatment of mild to moderate disease. (39) Because the effect of BPO on *P acnes* is a direct toxic effect rather than antibiotic, resistance has never been reported.

BPO is an excellent medication for patients with mild comedonal or inflammatory acne, a finding supported by several trials. (40)(41) BPO is available both with and without a prescription in concentrations ranging from 2.5% to 10%. Products sold over the counter include soaps, creams, washes, lotions, and gels. The prescription form generally involves a gel vehicle for enhanced efficacy or combines the BPO with another topical agent, such as an antibiotic or a retinoid, for enhanced ease of use and improved patient compliance. BPO, in 2.5% and 5% gels, was superior to vehicle for comedonal acne in several studies. (42)(43) For most patients, a single daily application of 5% is sufficient.

In addition to stinging, peeling, and burning sensations, which can be mitigated with noncomedogenic moisturizers and decreased frequency or nighttime use, patients should be warned that this product may bleach towels, bedding, and clothing. Rarely, BPO can cause an allergic contact dermatitis presenting with significant erythema, pruritus, and swelling. In such patients, BPO-containing products should be avoided. (44)

BPO has also been used in combination with a variety of other products conveniently available in the same vehicle. In a 2015 study by Kawashima et al (45) of 1.2% clindamycin and 3.0% BPO, 800 Japanese patients were randomized to receive clindamycin alone twice daily, clindamycin and BPO once daily, or clindamycin and BPO twice daily. Both combination products outperformed clindamycin on its own, with earlier onset of action and an acceptable tolerability profile in this population. (45)

Topical Antibiotics

Most topical antibiotic regimens use either clindamycin or erythromycin. As cited previously herein, topical antibiotic products are usually combined with BPO or a retinoid product.

Two well-designed double-blind, split-face studies compared tolerability of adapalene 0.3%/BPO 2.5% gel against clindamycin/BPO 3.75% gel in patients with moderate to severe acne. Despite having the lower concentration of BPO, the combination with the retinoid was associated with more burning and stinging. (46) The timing end

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point was 21 days, and we do not know whether patients might adapt and experience less irritation if given a longer time frame.

In the interest of antibiotic stewardship, prolonged antibiotic (topical or oral) monotherapy should be avoided whenever possible. Adding BPO to a regimen that includes antibiotics will not only be an additive acne treatment but will also reduce the risk of bacterial resistance. (47)(48)

Dapsone is the newest of the topical antibiotics and is a sulphonamide drug that exerts its antibiotic effects by inhibiting bacterial synthesis of folic acid. It also exhibits anti-inflammatory effects by targeting the neutrophil and thereby decreasing inflammation. It is available in 5% to 7.5% gel formulations for patients older than 12 years. A large double-blind, vehicle-controlled trial that included 2,238 patients 12 years and older with moderate acne as measured by a dermatologist was conducted using a validated scale. Patients were randomized to receive topical 7.5% dapsone gel or vehicle over a 12-week period, (49) and improvement was measured by looking at both inflammatory and noninflammatory lesion counts. Efficacy and tolerability were both acceptable using the once-daily 7.5% gel, with most patients reporting no to mild symptoms of drying. Once-daily dosing is an alternative to the twice-daily dosing of the 5% dapsone gel.

Patients should be warned about peeling and erythema at the application sites. The drug is safe to use in patients with glucose-6-phosphate dehydrogenase deficiency. (50)

Topical Retinoids

Derived from vitamin A, retinoids are a family of synthetic compounds that play a role in cell differentiation and growth. Retinoids bind to specific retinoid receptors in the nuclei of keratinocytes; of most interest are the retinoic acid receptors and retinoid X receptors. These medications are extremely effective at normalizing the exfoliation of the epithelial lining of the follicle and are also comedolytic. Improved exfoliation discourages follicular plugging, thereby preventing the formation of microcomedones (thus decreasing future true comedones and inflammatory lesions) and also promote the clearance of existing lesions. (51) In addition, retinoids help create an aerobic environment, which is noxious to *P acnes,* and block several important pro-inflammatory pathways known to contribute to acne, such as the TLR and activator protein 1 pathways. (52)

Tretinoin is a first-generation retinoid. It is extremely photolabile and recommended for nighttime use. Tazarotene and adapalene, classified as third-generation retinoids, are more receptor selective. Adapalene, available in 0.1% and 0.3% formulations, specifically binds to retinoic acid receptor γ. It is the most light stable of the topical retinoids and is the least susceptible to oxidation by BPO, justifying its role in popular combination therapies.

Topical retinoids are used once daily to the affected area as a field treatment (applying the product to a more extensive high-risk zone as part of preventive therapy rather than only treating individual lesions). Retinoids are encouraged for use at night to minimize photodestruction, and patients are counseled that it may take several weeks before they start to see improvement in their complexion. Patients should also be aware that during the first month of therapy there may be a paradoxical worsening of their acne as the drug encourages loosening of deeper comedones, which then come to the surface.

Adverse effects of retinoids include peeling and irritation, and many patients must start with low concentrations of the medicine or less frequent applications, working their way up to higher concentrations or more frequent applications. Daytime moisturizers and sunscreen are important adjuncts. All vitamin A derivatives are designated as category C or X, and all women of childbearing potential should be made aware of this with appropriate contraceptive counseling. Patients with atopic dermatitis may require milder or less frequent retinoids (eg, every second or third night instead of nightly) because their skin tends to be more easily irritated. Patients are often advised to avoid waxing, laser therapy, electrolysis, and exfoliation at treated sites because the retinoids, in part, can reduce the protective stratum corneum layer, thus increasing risk of damage from such agents.

Combination Treatment

Combination products, in which more than 1 medication exists in a single vehicle, have the advantage of using multimodal therapy with greater efficiency and, therefore, improved compliance. (53) These are popular products and incorporate medications that address different etiologic factors of acne and can be used in mild-moderate disease and as adjuncts to systemic treatment for more severe cases. Combinations include BPO with a topical antibiotic (such as erythromycin or clindamycin) or a retinoid, or an antibiotic with a retinoid; evidence of effectiveness is mentioned previously herein. These products are often more costly than single-medication products but are also more convenient. They are appropriate as first-line therapy options for all severities of acne and are recommended in the latest comprehensive review on the management of acne in the *Journal of the American Academy of Dermatology.* (54)

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Systemic Treatment Options

Antibiotics. Used for their anti-inflammatory as well as their *P acnes* antimicrobial abilities, antibiotics are useful treatments in the armamentarium against acne, thereby targeting 2 of the 4 main causes.

The tetracyclines inhibit bacterial protein synthesis, leading to a bacteriostatic mechanism of action. They are the most commonly used antibiotics for the treatment of acne, although dental staining in children younger than 9 years precludes their use in this age group, and they should not be given to pregnant or breastfeeding women. The tetracyclines generally should not be taken with food, except doxycycline to protect against esophagitis. The most common adverse effects are photosensitivity, gastrointestinal upset, and, rarely, pseudotumor cerebri.

Doxycycline is commonly used in 2 doses: 50 to 100 mg daily or twice daily, and 40 mg daily as an extended-release therapy (which was originally introduced to mitigate its gastrointestinal symptoms). Although it is subantimicrobial, low-dose doxycycline was hypothesized to be helpful in the treatment of acne after its success in rosacea treatment. A 2015 randomized controlled trial (which included children 12 years and older; average age, 19 years) was designed to test the efficacy of doxycycline 40 mg once daily, doxycycline 100 mg once daily, and placebo for moderate to severe acne. A total of 662 patients were randomized in a 1:1:1 manner for 16 weeks. Both dosages were superior to placebo regarding inflammatory lesion count, and both dosages were comparable in the improvement of total number of lesions and reduction of inflammatory lesions. Adverse effects (most commonly headache, nausea, and vomiting) were reported more often in the 100-mg group. The authors concluded that the 40-mg extended-release dosage of doxycycline is an effective and safe option for those with inflammatory acne lesions. (55)

Minocycline is used to treat a variety of dermatologic problems, including acne vulgaris, perioral dermatitis, and rosacea. It is the most lipophilic of the tetracyclines, achieving significant levels in the pilosebaceous unit and reaching high concentrations in the skin and nails. For acne, it is typically prescribed as 50 to 100 mg once daily for approximately 12 weeks or as an extended-release formula. (56) Major adverse effects of minocycline include nausea, vomiting, and dizziness; phototoxicity; blue-black pigmentation of the skin, nails, teeth, bones, and mucous membranes (57); a minocycline-induced lupuslike reaction (58); and drug reaction with eosinophilia and systemic symptoms (DRESS). (59) It is for these reasons that the authors of the latest Canadian clinical practice guidelines for acne in 2015 prefer tetracycline or doxycycline for the treatment of extensive moderate papulopustular acne. (60) Minocycline crosses the blood-brain barrier and should not be used in combination with isotretinoin owing to the risk of pseudotumor cerebri. Death is reported once in the literature (61) and twice in online articles found through common search engines. (62)(63) Minocycline hypersensitivity syndrome usually occurs within the first 6 to 8 weeks of therapy, beginning with flulike malaise and a morbilliform rash. End organ failure most commonly involves the liver but can manifest itself as kidney failure, myocarditis, thyroiditis, cerebritis, or pneumonitis. The latest Cochrane review, published in 2012, looked at minocycline's efficacy and safety and concluded that it did not outperform other tetracycline antibiotics as once believed. It may also have more safety concerns than the other tetracyclines, (64) although it is now less expensive.

Treating acne with oral antibiotics alone should be avoided so as to prevent antibiotic resistance.

Hormone Treatment Options. Several controlled trials have reported the positive effect of oral contraceptive pills on acne, (65)(66) and postmenarchal female patients with acne may benefit from hormonal treatment of their acne with the aim of reducing the stimulation of the sebaceous glands and thereby decreasing sebum production. This treatment is especially helpful when presented with the patient with older-onset acne (>25 years old), which is located primarily on the lower face and jawline, or who complain of menstrual flare. (67) Hormone therapies are divided into 2 categories: androgen synthesis inhibitors (in which estrogen and progesterone combination oral contraceptive pills are included) and androgen receptor antagonists (which include spironolactone, flutamide, and cyproterone acetate). The latter are particularly useful if acne is the result of an endocrinologic abnormality such as polycystic ovarian syndrome.

Treatment typically requires 3 to 6 months until improvement is seen, and patients should be warned that acne can return after treatment cessation. Contraindications to this treatment include patients older than 35 years, those who are active smokers, and patients with a history of venous thromboembolism or hypercoagulability.

Isotretinoin. Isotretinoin (13-cis-retinoic acid), an oral retinoid, is indicated for the treatment of nodulocystic acne and is the most effective treatment for severe and recalcitrant disease. (68) It is the only medication that affects all components of the acne tetrad and the only medication with curative potential, although disease recurrence after cessation is possible. Isotretinoin does not bind to retinoid receptors but rather is metabolized to tretinoin,

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which then binds to retinoic acid receptors. Tretinoin is extremely effective at decreasing sebum production by inducing apoptosis of the sebocytes, (69) and there is evidence that it also alters the bacterial environment of *P acnes*. (70)

Medication dosing has been found to be most effective with daily doses of 0.5 to 1.0 mg/kg per day or a total cumulative dose of 120 to 150 mg/kg over the treatment duration (usually approaching 20 weeks). Newer, off-label trends include using lower-dose therapy often well below the standard dose. (71)(72) Although isotretinoin is usually reserved for severe and recalcitrant disease, there have been studies looking at this "low-dose" and also "intermittent" regimen in moderate acne over the past 10 years with some evidence to support both efficacy and fewer adverse effects.

All patients will experience some sort of generalized skin and mucous membrane dryness while receiving isotretinoin. Cholesterol and liver enzyme abnormalities may occur but are typically transient, although they should be monitored. (73) Baseline laboratory tests are recommended monthly for 3 months and then every 3 months thereafter, although screening for pregnancy in females should be monthly. Muscle aches, decreased night vision, and photosensitivity are also reported. Again, this drug should never be used in combination with a tetracycline antibiotic. There may be a connection to depressed mood, but a causal linkage of this medication to suicidal ideation and major depressive disorder has not been definitively proved, (74) and, perhaps unsurprisingly, several studies have demonstrated an improvement in patient quality of life and depression scales as their acne improves. (75)(76) Patient mood should be documented, and those with depressive symptoms should be assessed for suitability of isotretinoin and monitored or managed accordingly. This may include the need to involve mental health professionals. In addition, some believe that there is an increased risk of developing inflammatory bowel disease (IBD), especially ulcerative colitis, in those using isotretinoin. This is supported by some literature but not others. A large 2010 case-control study by Crockett et al (77) looked at more than 8,000 patients with IBD and assessed isotretinoin exposure. They found a positive correlation with the development of IBD and exposure especially at higher doses and longer durations. (77) Countering this hypothesis is a large population-based study that looked at 2,008 patients with IBD. The authors were unable to prove that a diagnosis of IBD followed a course of isotretinoin, although they emphasized that we do not fully know the impact of isotretinoin on the gut. (78) A 2016 meta-analysis of controlled studies concluded that isotretinoin was not associated with an increased risk of ulcerative colitis or Crohn disease, (79) but debate remains, especially when looking at confounding variables such as severity of acne and past acne treatments, such as using antibiotics. As of now, there is no clear evidence of a causal link between isotretinoin therapy and IBD.

Being derived from vitamin A, isotretinoin is teratogenic, and rigorous counseling regarding pregnancy prevention is mandatory for female patients. Two simultaneous forms of birth control are recommended at the time of writing the prescription, and pregnancy tests should be performed monthly. American practitioners are also required to enroll female patients in the iPLEDGE program (a mandatory distribution program in the United States for isotretinoin). (80)

Historically, patients treated with isotretinoin were counseled to avoid dermabrasion and other resurfacing techniques until 6 to 12 months after completion of therapy because of the perceived risk of difficulty healing or keloid scarring. An excellent 2017 review in *JAMA Dermatology* looked critically at procedures during isotretinoin therapy (81) and suggested that this notion is too cautious. A panel of American experts studied publications reporting 1,485 procedures and concluded that there was insufficient evidence to support delaying many procedures during the 6- to 12-month abstinence recommendation. Based on the available literature, only caution against mechanical dermabrasion and ablative laser use was recommended. We must emphasize that further work is needed in this area, and we suspect that there will be more prospective trials regarding procedures and isotretinoin therapy in the future.

Physical Treatment

Comedo Extraction. Using a specialized comedo extraction device, the dermatologist can physically remove debris from comedones, improving the appearance of a patient's acne and enhancing topical treatment penetration. This procedure is especially beneficial for deep or persistent comedones but should not be performed on inflamed lesions. Closed comedones may also be nicked with a sterile blade to ease expression of their contents. These procedures can produce bruising and potentially scars.

Intralesional Corticosteroid Injection. An injected high concentration of corticosteroid into a nodulocystic lesion can ameliorate its appearance within 48 to 72 hours. (82) A corticosteroid, usually triamcinolone 10 mg/mL, is injected directly into a nodule with the aim of flattening the lesion and decreasing surrounding inflammation.

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Adverse effects, as with any corticosteroid, include atrophy, telangiectasia, striae, and pigmentary changes. It should not be offered as a treatment for widespread nodulocystic acne, and there are reports of systemic absorption of the drug. (83)

Cryotherapy. Occasionally cryotherapy has been used in the treatment of acne, but current supportive literature is lacking.

MAINTENANCE

Acne is a chronic disease, and many individuals experience lesions well into adulthood. (2) Each treatment should be trialed for 2 or 3 months and then advanced or tapered depending on clinical response. (62) During the visit, evaluation of tolerance and compliance to the current regimen should be noted. Poor compliance might be improved with combination products. Excessive dryness or irritation may be improved by lowering the concentration of a product, changing the base from a more drying one, such as a gel or solution, and using a more hydrating base such as a cream, or reducing frequency of application.

Long-term maintenance outcomes have been minimally studied, but general consensus is that oral medications, except for possibly oral contraceptives, have a finite treatment time. Topical medication should be introduced once the disease is sustainably under control. Because topical retinoids act on the microcomedone, they are popular preventive products and are often used for long-term maintenance. Two trials support this, showing continued control of previously moderate to severe acne for 4 to 6 months after discontinuing systemic antibiotic therapy. (84)(85)

Postacne Scar Treatment

Lingering signs of acne lesions are common and can be distressing. Several techniques try to ameliorate the appearance of acne scars, but most split-face studies have unpredictable results, resulting in no gold standard as of yet.

Cosmetic camouflage helps with erythema, postinflammatory dyspigmentation, and, to a more modest extent, atrophic scars. (86)(87) Dermabrasion is a mechanical technique whereby a motorized tool coated with an abrasive substance is used to remove the superficial layers of skin, creating a wound, and thereby encouraging healing and laying down of new collagen. Edema and erythema may persist for weeks after this intervention. (88) Dermal fillers, made of several materials but most commonly hyaluronic acid, can be injected into acne scars. These procedures, most often used in the adult population, are an expensive option and must be repeated every 6 to 9 months to achieve a sustained effect. (89)

Subcision introduces a small needle into the periphery of an atrophic scar and is moved back and forth with the aim of releasing a tethered base. Subsequent bleeding is also thought to recruit new collagen formation, which can act as a filler to improve scar appearance. There are a few split-face randomized controlled trials that show efficacy and good tolerability of this technique, although these studies have small sample sizes. (90)(91)

Laser and Light Treatment

Laser and light therapies are 2 modalities sometimes used in acne management. Some are used to reduce lesion count and erythema, and others are better for treating scarring.

For active lesions, pulsed dye laser (PDL) is Food and Drug Administration (FDA) approved for inflammatory acne sequelae, although data are conflicting. (92) PDL is most commonly used and indicated for vascular lesions: its chromophore is hemoglobin. It targets the erythema of acne. (93)(94) Seaton et al (92) randomized 41 patients to receive PDL or a sham treatment once and assessed patients at 2-week intervals until 12 weeks after therapy. They noted a significant improvement in lesion count and erythema, but Orringer et al (95) noted no difference in their split-face study of 40 patients and could not definitively recommend PDL. A more recent 2017 blinded Thai study randomized 30 adolescents aged 13.0 to 21.6 years to receive a split-face treatment of 595-nm PDL versus no treatment. There was no statistically significant decrease in acne erythema, as in Orringer et al's study, but the active papule count was significantly improved on the PDL side after 4 weeks and there was high reported patient satisfaction. (96)

Light-based therapies (usually red and blue light) are thought to treat active acne through reduction of *P acnes* levels by targeting their bacterial porphyrins. (97) Both red and blue may be helpful in decreasing inflammation and lesion count, but many trials looked at a very small number of participants without a control group. (98)(99) It seems that the improvement is likely only marginal, based on a 2016 Cochrane review. (101)

Laser treatment of acne scars is most commonly studied using fractional carbon dioxide lasers that penetrate only the epidermis and upper dermis, creating thermolysis and encouraging growth of new collagen. (100) There are many small, heterogeneous studies that support the use of fractional laser, and it may well be a promising option,

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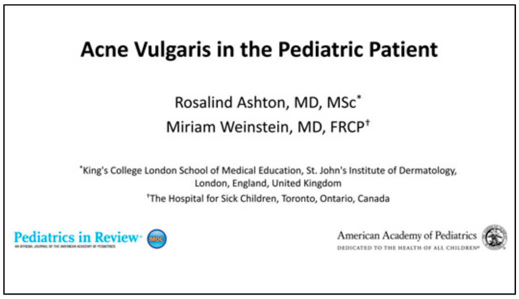
(102)(103) but patients should expect postprocedure edema and erythema, and practitioners should be wary of patient skin type because some may experience substantial postinflammatory dyspigmentation.

Summary

- Acne vulgaris is a common problem in pediatric practice with important psychosocial consequences.
- Acne vulgaris is caused by the tetrad of inflammation, association with *Proprionibacterium acnes*, abnormal keratinocyte shedding, and increased sebum production. Management aims to educate the patient; treat comedones, inflammatory papules, and pustules; and prevent scarring.
- There is high-quality evidence in randomized controlled and split-face trials that mild to moderate disease can be ameliorated with first-line topical therapies, including acids, benzoyl peroxide, topical antibiotics, and topical retinoids. (40)(41)(44)
- In women who can take the oral contraceptive pill and who experience premenstrual flares, especially along the jawline and lower face, we have presented 2 randomized controlled trials supporting use of the oral contraceptive pill. (59)(60)
- Severe disease warrants systemic treatment, including oral antibiotics (49) or isotretinoin; a low-dose or intermittent regimen with isotretinoin seems to have good efficacy and tolerability. We expect to see more studies addressing this topic in the near future. (65)(66)
- Based on consensus there is good evidence that topical retinoids are the treatment of choice for maintenance therapy. (79)(80)
- All medications have potential adverse effects, which should be discussed with the patient, and a trial of medication should be given an appropriate amount of time to exert its effects (ie, ≥6 weeks).
- Postacne sequelae can be treated with a variety of modalities, including peels, physical techniques, and lasers, although trials of these modalities are considered low quality due to lack of reproducibility and small study sizes.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/40/11/577.supplemental.



Acne Vulgaris in the Pediatric Patient

Rosalind Ashton, MD, MSc[*]
Miriam Weinstein, MD, FRCP[†]

[*]King's College London School of Medical Education, St. John's Institute of Dermatology, London, England, United Kingdom
[†]The Hospital for Sick Children, Toronto, Ontario, Canada

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1. A 6-year-old boy is brought to the clinic for evaluation of mild acne. As an infant he had acne that resolved on its own. Recently, the mother has noticed that the acne has recurred. In addition to assessing height and weight, and a complete history and physical examination, which of the following is the next best step in the management of this patient?
   A. Obtain total and free serum testosterone, dehydroepiandrosterone, 17-hydroxyprogesterone, and luteinizing hormone/follicle-stimulating hormone levels.
   B. Reassurance. No treatment is necessary because this condition is benign and will spontaneously resolve.
   C. Start the patient on benzoyl peroxide facial wash and anti-acne soap.
   D. Start the patient on topical retinoid.
   E. Skin biopsy of 1 of the lesions.
2. A 13-year-old girl is brought to the clinic for a health supervision visit. She reports that she started noticing some acne over the past 9 months and is bothered by it. On physical examination she has multiple microcomedones and comedones over the face and upper chest with few pustules seen. No nodules or scarred lesions are noted. In addition to pharmacologic treatment, which of the following measures is the most appropriate to recommend at this point for this patient?
   A. Adopt a high glycemic index diet.
   B. Gentle cleaning of the face once or twice a day before application of topical agents.
   C. Gluten-free and dairy-free diet.
   D. Use an abrasive soap scrub to remove debris.
   E. Wash the face multiple times a day.
3. A 13-year-old girl with mild comedonal acne and oily skin is brought to the clinic for management. She denies sexual activity. Her sexual maturity rating is Tanner stage 2-3. Besides nonpharmacologic treatment, which of the following is the best next step in the management of this patient?
   A. Medium-strength topical retinoid daily.
   B. Mild retinoid ointment every other night to twice per week.
   C. No treatment should be added at this point. Continue washing the face twice a day.
   D. Oral doxycycline.
   E. Oral isotretinoin.
4. A 14-year-old boy was seen in the clinic a year ago for a health supervision visit. At that time he was noted to have mild acne and was well maintained on benzoyl peroxide washes and anti-acne soap. He returned to the clinic 2 weeks ago. At that time, the examining physician noted that his acne has now progressed to moderate acne, which remained comedonal with no evidence of pustules. The patient was started on topical benzoyl peroxide and retinoids. He returns to the clinic today because of no improvement. The parents are wondering if he needs to be seen by a dermatologist. Physical examination shows no signs of worsening of his acne from his visit 2 weeks earlier. Which of the following is the most appropriate next step in the management in this patient?
   A. No referral is needed. Ensure compliance with the current treatment and use for at least 6 to 8 weeks.
   B. Refer to dermatology.
   C. Start hormone therapy and refer to dermatology.
   D. Start oral antibiotics and refer to dermatology.
   E. Start oral isotretinoin and refer to dermatology.

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5. A 15-year-old girl is brought to the clinic for evaluation and treatment of her acne. On physical examination she is noted to have severe nonnodulocystic acne. She has been previously referred to dermatology and was prescribed oral isotretinoin. The patient admitted that she has not filled the prescription as she is not comfortable taking oral isotretinoin due to adverse effect concerns. She was wondering whether there are other suitable alternatives. Her current treatment regimen includes benzoyl peroxide, topical isotretinoin, and oral antibiotics for breakthrough lesions. Which of the following is the most appropriate plan of care for this patient?

   A. Add oral contraceptives to her current regimen.
   B. Add topical dapsone to her current regimen.
   C. Caution her that oral isotretinoin is the only best option for long-term control for her.
   D. Continue her current treatment regimen.
   E. Recommend a trial course of topical adapalene with benzoyl peroxide gel and oral antibiotics.

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Index of Suspicion

1

Acute Respiratory Failure in a 1-month-old Girl

Tara Glenn, MD,* Anne Kim Mackow, MD, MPH,[†] Jill Shivapour, MD,*
Moira Crowley, MD*

**Department of Pediatrics and* [†]*Department of Pediatric Surgery, University Hospitals Rainbow Babies and Children's Hospital, Cleveland, OH*

EDITOR'S NOTE

It is good to be thankful. Whether in mindfulness training, historical contexts, or religious beliefs, the values of gratitude are widely espoused. Last month, readers in Canada celebrated a national day of Thanksgiving, and, this month, readers of *Pediatrics in Review* in the United States are celebrating Thanksgiving.

There is much for which to be thankful. Some gratefully celebrate personal blessings and accomplishments, while others are thankful for the provision of food, water, and shelter. Getting even more basic, we can be grateful for airways, breathing, and circulation. In this month's *Index of Suspicion* cases, we follow the thought processes of clinicians helping children with altered respiratory statuses. Continuing to update our medical knowledge and skills, we provide care for which our patients and their families can be grateful.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A 1-month-old girl presented to the emergency department with respiratory failure. She was a full-term infant born after an uncomplicated pregnancy and delivery requiring no resuscitation. At 30 hours of life she had a choking spell with a feed and was transferred from the maternal ward to the NICU. A chest radiograph was performed and showed vertebral body segmentation anomalies in the thoracic spine, clear lung fields, and a nasogastric tube in the stomach. An echocardiogram demonstrated an atrial septal defect, a ventricular septal defect, and a bicuspid aortic valve. Due to the multiple observed anomalies, further diagnostic testing was performed to evaluate for a unifying diagnosis or a genetic syndrome. These tests included an eye examination, renal and head ultrasonography, brain magnetic resonance imaging, upper gastrointestinal series, chromosomal microarray, and karyotype; all results were normal. Due to her choking, a swallow study was performed with occupational therapy and demonstrated aspiration of feeds of all thicknesses. She was discharged on digoxin, furosemide, and full nasogastric feeds.

AUTHOR DISCLOSURE Drs Glenn, Mackow, Shivapour, and Crowley have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Two weeks after hospital discharge she started coughing, which was worse when feeding or in a supine position. One coughing episode was associated with emesis and respiratory distress, and the family brought her to the emergency department. On arrival, she was in severe respiratory distress and required intubation. Examination was notable for tachycardia, 2/6 systolic murmur, decreased air entry with coarse breath sounds, hepatomegaly with liver edge 2 to 3 cm below the costal margin, pale skin, and capillary refill of 3 to 5 seconds. Respiratory failure continued to worsen and was accompanied by frequent desaturations requiring suctioning and manual positive pressure ventilation. Of note, suctioned secretions periodically resembled formula. She also had intermittent gastric distention despite appropriate positioning of the endotracheal tube (Fig 1). On rigid bronchoscopy she was found to have an H-type tracheoesophageal fistula (TEF) (Fig 2) and, thus, the diagnosis of VACTERL association was made. She underwent repair of the TEF; however, she died of complications related to her disease process.

DISCUSSION

The constellation of symptoms, including cyanosis during feeds, aspiration, abdominal distention with positive pressure ventilation, and suctioning of formula from the endotracheal tube, were suspicious for an H-type (congenitally isolated) TEF. Previous radiographic studies demonstrated the nasogastric tube in the stomach, thus esophageal atresia was not present.

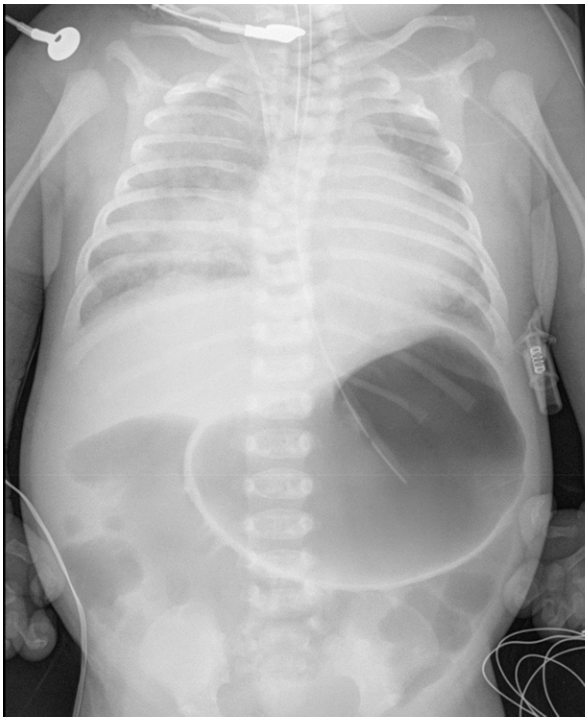

Figure 1. Radiograph showing gastric distention.

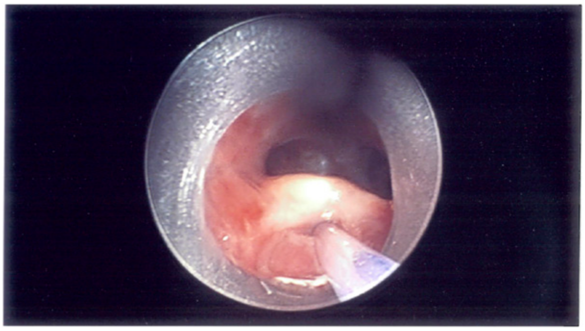

Figure 2. Findings on bronchoscopy.

The esophagus and trachea develop from the primitive foregut at 4 to 6 weeks' gestation. A ventral diverticulum derived from the caudal part of the foregut forms the trachea and lung bud. The tracheoesophageal fold fuses into a septum that divides the foregut into the ventral laryngotracheal tube and the dorsal esophagus. (1) If this separation is incomplete, TEF results.

The most common type of TEF is esophageal atresia with distal TEF, which is typically diagnosed early in the neonatal period. (2) Congenital isolated TEF, also known as H-type or N-type, due to the downward angle of the fistula with the esophageal orifice inferior to the tracheal orifice, (3) is less common and composes 4% to 5% of all TEFs. (1) Presentation for this type of TEF includes a classic triad of symptoms: recurrent respiratory infections, aspiration during feeding with cyanosis, and abdominal distention. (3)(4) TEF is frequently associated with other anomalies, including cardiac, gastrointestinal, genitourinary, and musculoskeletal anomalies, and with genetic syndromes. (4) TEFs are usually diagnosed in the neonatal period because most cases are associated with esophageal atresia. However, isolated TEF frequently has a delayed diagnosis that is attributed to the subtlety of presentation, symptoms masquerading as other disease processes, and unsatisfactory diagnostic testing. (3)(4)

The constellation of vertebral defects, anal atresia, cardiac defects, TEF, renal anomalies, and limb abnormalities is known as VACTERL association. This is the most common constellation of defects associated with TEF, although affected infants have also been reported to have trisomy 13, 18, or 21; Pierre Robin sequence; 22q11 deletion syndrome; CHARGE (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear

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abnormalities) syndrome; Fanconi anemia; and polysplenia syndrome. (1) Diagnosing VACTERL requires 3 of these characteristic features, although patients may have other anomalies outside of this group. (1) TEF occurs in 50% to 80% of patients with VACTERL association. There is no specific genetic abnormality associated with VACTERL, and the association is thought to be the result of both genetic and environmental influences during development. The association is typically sporadic and does not have a clear inheritance pattern.

TEF has many associated complications, including recurrent pneumonia (which can lead to bronchiectasis if left untreated), acute lung injury and acute respiratory distress syndrome, lung abscess, poor nutrition, esophageal dysmotility, respiratory failure, and death. Overall survival is 80% to 90%, but this rate decreases when other congenital anomalies are present. Major postoperative complications include recurrent fistula and tracheal stenosis. Long-term complications include esophagitis, gastroesophageal reflux disease, Barrett esophagus, and hiatal hernia.

The diagnosis of TEF is made by a contrast tube esophagogram or rigid bronchoscopy. During a tube esophagogram, contrast is instilled into a catheter placed in the esophagus with the patient prone and in the Trendelenburg position. This allows contrast to flow “retrograde” through the angled fistula from the posterior esophagus to the anterior trachea. (1) This procedure carries the risk of respiratory compromise if a fistula is present. If the contrast evaluation is negative but clinical concern remains, or the patient is too unstable to have the contrast study, then rigid bronchoscopy with esophagoscopy is recommended. (5) Bronchoscopy is useful to delineate the anatomy of the TEF and assist in planning the approach for surgical repair. Before repair, infants should be evaluated for other anomalies, including an echocardiogram to evaluate for congenital heart disease and determine aortic arch sidedness for surgical planning. Infants should be kept upright as much as possible. Gastric acid blockade should be instituted to reduce any injury from gastric secretions in the airway. (1) Primary repair is indicated in otherwise well infants. If repair is delayed due to low birthweight, pneumonia, or other anomalies or complications, patients should be kept on parenteral nutrition or a gastrostomy tube should be placed for feeding. (1) Ongoing mechanical ventilation after repair is associated with fistula recurrence and complications. Therefore, patients should ideally be weaned off mechanical ventilation before repair if the patient’s clinical condition permits.

Lessons for the Clinician

- Consider a diagnosis of congenital isolated tracheoesophageal fistula (TEF) in infants with recurrent pneumonia, coughing with feedings, or abdominal distention.
- Consider TEF in a neonate with aspiration and vertebral anomalies.
- The initial diagnostic test is typically tube esophagography, but the diagnosis can also be made with rigid bronchoscopy and esophagoscopy.
- Consider VACTERL association in patients who present with any type of TEF.
- Diagnostic tests for congenital isolated TEF have a high rate of false-negatives; if clinical suspicion persists, repeat diagnostic evaluation.

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2 Respiratory Failure and Multiple Organ System Dysfunction in a 7-day-old Infant

Kelsey Poisson, MD,* Jen-Jar Lin, MD,† Ashton Chen, DO,†
Michael C. McCrory, MD, MS†‡

*Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
†Department of Pediatrics and ‡Department of Anesthesiology, Wake Forest Baptist Medical Center, Winston-Salem, NC

PRESENTATION

A 7-day-old boy is referred to the emergency department by his pediatrician for increased work of breathing. He was born at 39 weeks' gestation by spontaneous vaginal delivery with prolonged rupture of membranes. His newborn nursery stay was uncomplicated, and the results of his congenital heart screen were normal. His mother reports difficulties with breastfeeding due to poor latch, for which he has been receiving supplemental formula. She also reports increased fussiness and "brownish-red spots" in his diapers. There is no cyanosis or choking during feeds. There is no history of fever, vomiting, diarrhea, rashes, cough, sick contacts, or decreased urine output.

On examination he is alert, afebrile, and mildly tachycardic, with a blood pressure (BP) of 70/22 mm Hg. Weight is 3,270 g (birthweight, 3,785 g). Oxygen saturation is 84% on room air and improves to 98% with supplemental oxygen. He is tachypneic, with subcostal retractions, grunting, and head bobbing during respirations. Lungs are clear to auscultation. Capillary refill is normal, and femoral pulses are strong. There are no rashes. Abdomen is soft, with mild hepatosplenomegaly.

Laboratory evaluation is notable for a white blood cell count of 28,000/μL (28×10^9/L), blood urea nitrogen level of 42 mg/dL (15.0 mmol/L), and creatinine concentration of 0.72 mg/dL (63.65 μmol/L). Results of cultures and viral studies are pending. Liver enzyme levels, troponin level, B-type natriuretic peptide level, prothrombin time, and D-dimer level are significantly elevated; ammonia level is 96.6 μg/dL (69 μmol/L). A capillary blood gas analysis shows mixed respiratory and metabolic acidosis with an elevated lactate level. A urine dipstick test shows 3+ protein, large blood, and nitrites, with white and red blood cells.

A chest radiograph demonstrates cardiomegaly and increased pulmonary vascularity (Fig 1). An echocardiogram reveals no patent ductus arteriosus or structural heart disease but is significant for moderate biventricular systolic depression and dilation with severe pulmonary arterial hypertension.

He is admitted to the PICU on broad spectrum antibiotics and high-flow nasal cannula for oxygen supplementation. Milrinone therapy is initiated due to depressed ventricular function. His BP subsequently increases to 127/89 mm

AUTHOR DISCLOSURE Drs Poisson, Lin, Chen, and McCrory have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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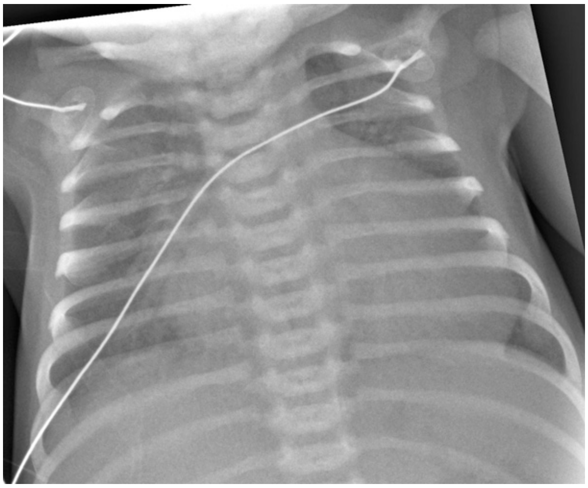

Figure 1. Chest radiograph demonstrating marked cardiomegaly with diffusely increased pulmonary vascularity.

Hg and is sustained. Within hours he is intubated due to worsening hypoxic respiratory failure. A subsequent imaging study reveals the cause of his multiorgan failure.

DISCUSSION

Hospital Course

This 7-day-old boy presented with multiorgan dysfunction, including hypoxic respiratory failure, heart failure (as evidenced by echocardiographic findings and hepatosplenomegaly), acute kidney injury (as evidenced by an elevated serum creatinine level for age and the presence of hematuria and proteinuria), and highly elevated liver enzyme levels with coagulopathy. The team initially suspected urosepsis as the underlying etiology based on urinary findings and clinical presentation. Other differential diagnoses included sepsis of another etiology, congenital heart disease, myocarditis, congenital viral infection, or metabolic disorder (such as organic acidemia, fatty acid oxidation defect, or mitochondrial disorder). Viral myocarditis with associated cardiac dysfunction remained a possibility, but results of viral studies (including herpes simplex virus from blood and cerebrospinal fluid, adenovirus from blood and urine, enterovirus from blood, and respiratory viral panel from nasal swab) were negative. Blood, urine, and cerebrospinal fluid cultures were also negative. Metabolic disorder was less likely given the absence of significant hyperammonemia, dysmorphism, or hypotonia, as well as rapid clearance of lactate. The newborn screen was later found to be normal except for a borderline acylcarnitine profile, which was not repeated due to the discovery of an alternate definitive diagnosis.

Renal ultrasonography was performed due to concern for urinary tract infection in a newborn. It showed an enlarged, echogenic left kidney and a possible partly duplicated right collecting system. Nephrology was consulted owing to these findings and a persistently elevated BP (>99th percentile for postconceptional age). (1) Four-extremity BPs were congruent. Repeated urinalysis on day 3 of admission showed only 3+ proteinuria and large blood with negative microscopic examination. Concern was raised for renovascular hypertension, and duplex ultrasonography of renal vasculature revealed critical stenosis of the left renal artery. Mesenteric duplex ultrasonography and magnetic resonance angiography were also performed, with magnetic resonance angiography (Fig 2) confirming the presence of left mid-distal renal artery stenosis with no other vascular anomalies. Plasma renin activity and aldosterone level were significantly elevated: renin, 1,333 ng/mL per hour (reference range, 2.35–37 ng/mL per hour), and aldosterone, 295 ng/dL (8,183 pmol/L) (reference range, 5–31 ng/dL [139–860 pmol/L]).

The Condition

Neonatal hypertension occurs in approximately 0.2% of neonates, where renovascular and renal parenchymal abnormalities constitute most cases. (2) Indwelling umbilical arterial catheter with associated thromboembolism is a common etiology; however, our patient had an umbilical

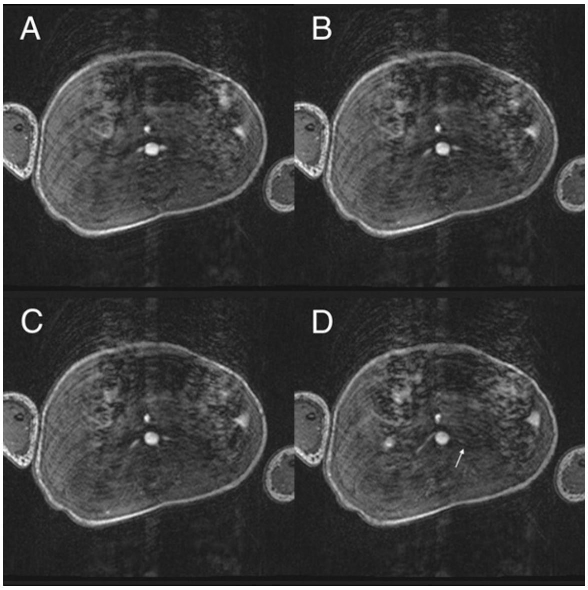

Figure 2. Magnetic resonance angiogram of the renal arteries using two-dimensional time-of-flight imaging. The renal arteries are followed from their abdominal aorta origin in sequential images A to D, with similar caliber observed bilaterally in the proximal images A to C. Attenuation of signal is noted in the mid-distal left renal artery in image D (arrow), indicating stenosis.

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line placed only after his initial presentation. Diagnostic evaluation for neonatal hypertension should be targeted at identifying possible underlying etiologies, beginning with 4-extremity BP to rule out aortic coarctation. (1) If underlying or secondary cardiac pathology is suspected, chest radiography and echocardiography may be useful. Abdominal examination should assess for flank masses or abdominal bruits. Laboratory evaluation may include complete blood cell count, electrolytes, blood urea nitrogen, creatinine, urinalysis, fractional excretion of sodium, thyrotropin and free T4, plasma fractional metanephrines and catecholamines, plasma renin activity, aldosterone, and cortisol to assess for intrinsic renal etiology, hyperthyroidism, pheochromocytoma, or congenital adrenal hyperplasia. Imaging should begin with renal ultrasonography with Doppler study to search for congenital renal anomaly or mass. Additional imaging studies may be needed, including abdominal computed tomography, vesicoureterography, magnetic resonance imaging/magnetic resonance angiography, or renal angiography to define renal/adrenal masses or vascular/urologic anomalies.

Renal artery stenosis is uncommon in the neonatal population and often presents with hypertension. In the setting of decreased renal perfusion pressure, the renin-angiotensin system is activated, causing vasoconstriction and aldosterone release with subsequent salt/water retention and hypertension. If uncontrolled, increased afterload and resulting cardiac strain can precipitate heart failure and pulmonary edema. Although no BPs were recorded in our patient's newborn nursery stay, we postulate that this mechanism was responsible for his presentation. Such cases have been described that presented with respiratory failure, heart failure, nephrotic syndrome, or a sepsislike picture. (3)(4)(5)(6)(7) Other renal anomalies, such as renal tubular dysgenesis, may exhibit a similar presentation. (8) Note that hypertension may not manifest until the presenting congestive heart failure or shock is addressed. (3) Our patient's BP rose from 70/22 mm Hg at presentation to 127/89 mm Hg with the administration of maintenance fluids, supplemental oxygen, and milrinone therapy. Renal artery stenosis in a pediatric population has also been described in association with congenital rubella, (9) neurofibromatosis 1, (10) tuberous sclerosis complex, (11) neuroblastoma, (12) retroperitoneal hematoma, (13) fibromuscular dysplasia, (3) and midaortic syndrome. (14)

Infants with BP greater than the 99th percentile for postconceptional age and signs of hypertensive emergency, such as encephalopathy, acute kidney injury, cardiac failure, or vascular injury, should receive continuous infusion of intravenous antihypertensive medications, such as nicardipine, labetalol, or esmolol. Once BP is better controlled, the patient can be transitioned to oral therapy. (15) Surgical nephrectomy may be curative if BP is unresponsive to medication.

Our patient's hypertension responded to a nicardipine drip. During his hospitalization, his acute kidney injury resolved, cardiac function improved, and he was extubated and weaned to room air. He was discharged on 0.2 mg/kg amlodipine twice daily and 0.04 mg/kg enalapril twice daily. At 2-month follow-up, his BP remained well-controlled, cardiac function had normalized, and renal function and urinalysis were normal.

Lessons for the Clinician

- Renal artery stenosis should be on the differential diagnosis of an infant with congestive heart failure in the absence of congenital heart disease.
- In the setting of heart failure due to severe arterial hypertension, elevated blood pressures may not be readily apparent until cardiac function improves.
- Signs of neonatal hypertension may initially be nonspecific, including feeding difficulties, irritability, apneas, seizure, or failure to thrive.
- Initial evaluation for neonatal hypertension should include 4-extremity blood pressures, chest radiography, echocardiography, complete blood cell count, electrolytes, blood urea nitrogen and creatinine, urinalysis with urine protein to creatinine ratio, thyroid function, and renal ultrasonography with Doppler study. Further evaluation should be guided by initial findings and clinical suspicion.
- Infants with sustained blood pressures greater than the 99th percentile for postconceptual age and signs of hypertensive emergency require continuous intravenous infusion of antihypertensive medications.

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Case 2: Respiratory Failure and Multiple Organ System Dysfunction in a 7-day-old Infant

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3 Persistent Fussiness in a 2-month-old Girl

Steven Loscalzo, MD,* Kelly Brower, MD,* Michael Del Vecchio, MD†

*Children's Hospital of Philadelphia, Philadelphia, PA
†St Christopher's Hospital for Children, Philadelphia, PA

PRESENTATION

A 2-month-old girl is referred from her primary care provider for evaluation of persistent fussiness. Symptoms began 2 days earlier. She had been evaluated by an urgent care center at the time of symptom onset. There she was diagnosed as having colic and given instructions for supportive measures at home. Since onset, she continues to cry for long stretches and is consolable only after being picked up or held semiprone. Her cry is softer than normal. Mother denies any fevers, cough, congestion, eye discharge, abdominal distention, discolored stool, or rashes. Despite being more difficult to console, she has continued to feed from both breast and bottle without a decrease in wet or dirty diapers.

Vital signs are as follows: temperature, 98.6°F (37.0°C); heart rate, 169 beats/min; respiratory rate, 40 breaths/min; blood pressure, 82/60 mm Hg; and oxygen saturation, 98% on room air. From the bedside, she is vigorous with an audible cry. The anterior fontanelle is open and flat. Respirations are unlabored without adventitious sounds or accessory muscle use. The abdomen is nontender with active bowel sounds and without any palpable masses or hepatosplenomegaly. Careful examination of the digits demonstrates no evidence of hair tourniquet. The remainder of the examination findings are within normal limits.

Plain films of the chest and abdomen are within normal limits. Blood and urine culture samples are collected. Laboratory evaluation reveals the following: a white blood cell count of 19,800/μL (19.8×10^9/L), with 72% neutrophils, 13% lymphocytes, 9% monocytes, and 0% monocytes; a hemoglobin level of 11.6 g/dL (116 g/L); and platelet count of 681×10^3/μL (681×10^9/L). Urinalysis of a catheterized urine sample reveals yellow color, cloudy appearance, specific gravity of 1.025, pH 6.0, negative leukocyte esterase and nitrite, and trace ketones. The C-reactive protein level is 8.2 mg/L (78.0 nmol/L).

She is admitted to a general pediatrics service for continued observation without initiation of antibiotic drug therapy. On the second day of admission she develops positional stridor, refusal of oral intake, and a low-grade fever of 100.8°F (38.2°C). Repeated laboratory studies are significant for a C-reactive protein level of 143 mg/L (1,361.9 nmol/L). An additional radiography study confirms the diagnosis (Fig) and prompts additional interventions.

DISCUSSION

The lateral neck radiograph demonstrated thickening of the retropharyngeal soft tissues with focal lucencies, likely representing air, compatible with a

AUTHOR DISCLOSURE Drs Loscalzo, Brower, and Del Vecchio have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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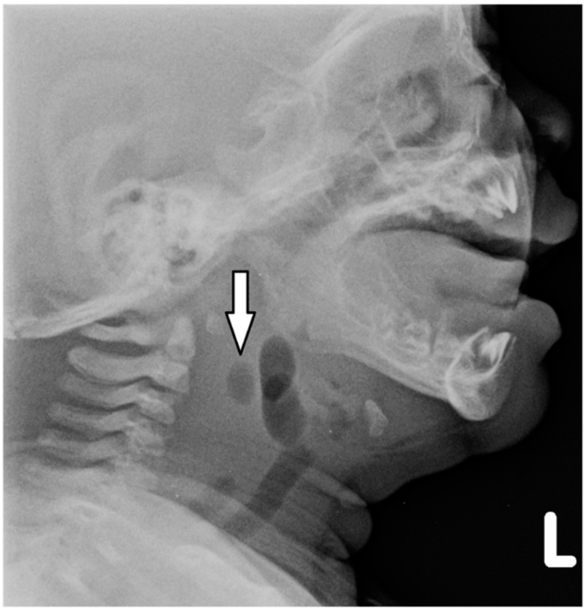

Figure. Lateral neck radiograph highlighting radiolucency in retropharyngeal space (arrow) concerning for free air.

retropharyngeal abscess. Cross-sectional imaging confirmed the suspected diagnosis, demonstrating ill-defined enlargement of the retropharyngeal soft tissue with fluid and gas causing anterior displacement of the trachea. In consultation with otolaryngology, she was transferred to the ICU for close monitoring, attempted surgical drainage, and an extended course of intravenous antibiotic agents, including vancomycin and ampicillin-sulbactam. She gradually recovered without any residual swallowing dysfunction. An esophagram demonstrated no evidence of diverticulum, and a follow-up outpatient direct laryngobronchoscopy demonstrated only mild soft tissue redundancy with mild tracheomalacia.

The Condition

Retropharyngeal abscesses form in the potential space between the posterior pharyngeal wall and prevertebral fascia occupied by the paramedial lymph node chains that filter lymph from the nasopharynx and paranasal sinuses. Simple infection or trauma can lead to lymph node enlargement, necrosis, and potential for phlegmonous change preceding frank abscess formation. Patients with a retropharyngeal abscess typically have a constellation of symptoms, including fever, neck pain or stiffness, and a change in voice quality. As symptoms progress, patients can develop difficulty handling secretions, odynophagia, and stridor with or without respiratory distress.

Untreated, retropharyngeal abscess can have severe clinical sequelae. The infection can serve as a nidus for septicemia. Localized swelling and inflammation can lead to airway obstruction, and in severe cases, erosion through the soft tissue can lead to thrombophlebitis of the internal jugular vein (Lemierre disease). The neonatal population in particular seems to be more vulnerable to direct extension into the mediastinum and the resultant mediastinitis or cavitary pneumonia. (1)(2)

Diagnosis

The diagnosis of retropharyngeal abscess is rare in infants younger than 3 months without a history of airway trauma. Reported symptoms include respiratory distress, poor feeding, and irritability with or without fever at the time of presentation. The diagnosis can be confirmed on a lateral neck radiograph with full neck extension, where evidence of widening of the retropharyngeal space or mass effect would be seen. Cross-sectional imaging can be a valuable tool in confirming the diagnosis and guiding potential surgical interventions. (3)

Treatment

All patients should be thoroughly assessed for indications of airway compromise requiring immediate attention. Broad spectrum antibiotic agents, with potential surgical drainage, remain the mainstay of management. Infections are typically polymicrobial, including *Streptococcus pyogenes,* non–group A *Streptococcus, Staphylococcus aureus* (methicillin susceptible and resistant), and anaerobic species, including *Prevotella, Bacteroides,* and *Peptostreptococcus.* (4)(5) Clindamycin or ampicillin-sulbactam provide adequate coverage in most scenarios, although the addition of vancomycin in the ill-appearing patient or in the patient with positive blood cultures is appropriate. Nearly 80% of patients with abscesses smaller than 20 mm improve within 48 hours with antibiotic drug therapy and conservative management alone. Patients with abscesses larger than 25 mm or those who fail to improve on antibiotic drug therapy are more likely to require surgical intervention. In all cases, the risk of iatrogenic injury from surgery needs to be weighed against the risk of antibiotic drug resistance and prolonged hospitalization. (6)

Differential Diagnosis

Persistent fussiness in infants with otherwise normal physical examination findings should raise the suspicion for serious underlying conditions. Focused history and examination looking for evidence of infection, accidental and nonaccidental trauma, corneal abrasions, hair tourniquets, or intestinal obstruction are always indicated.

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Retropharyngeal abscesses, although rare in neonates, can have an indolent presentation and should be considered in the setting of persistent oral refusal, fussiness, and upper airway signs.

Lessons for the Clinician

- Acute onset of fever, odynophagia, neck stiffness, hoarse voice, and difficulty with secretions should raise the suspicion for a potential retropharyngeal abscess. Children younger than 6 months may have a more insidious onset at the time of presentation.
- Ensuring a stable airway should take priority in all patients; the diagnosis can be confirmed with lateral neck radiography or cross-sectional imaging.
- Conservative management with targeted antibiotic drug therapy may be appropriate for stable children with small abscesses; however, children with protracted courses or large collections should be evaluated by otolaryngology for possible surgical intervention.

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Case 3: Persistent Fussiness in a 2-month-old Girl

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Case 3: Persistent Fussiness in a 2-month-old Girl

Steven Loscalzo, Kelly Brower and Michael Del Vecchio

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Index of
Suspicion

4 Vomiting and Tachypnea in a 9-week-old Girl

William R. Otto, MD,* Sarah Orr, DO,[†] Jennifer W. Boyd, DO*[‡]

*Department of Pediatrics and [‡]Division of Endocrinology, Children's Mercy Hospital, Kansas City, MO
[†]Department of Pediatrics, University of Kansas Medical Center, Kansas City, KS

PRESENTATION

A previously healthy 9-week-old girl presents to the emergency department with vomiting and new onset of tachypnea. She was seen in the emergency department 3 days before this visit, monitored, and discharged with a diagnosis of viral gastroenteritis. Her symptoms continued, and she was again seen in the emergency department the next day. An abdominal radiograph revealed a nonobstructive bowel gas pattern. Abdominal ultrasonography was performed to assess for pyloric stenosis and was normal. She was discharged after she was able to drink an oral electrolyte solution without vomiting. She presents again with continued nonbloody, nonbilious vomiting, although her mother is also concerned because she is having abnormal breathing. A review of systems reveals poor feeding and decreased activity. A review of her growth chart shows an 800-g weight loss in 3 days. There are no sick contacts or recent travel. She was a term infant and has been healthy until now. Her parents are second cousins, but there is no family history of significant medical problems. She has recently received her 2-month vaccinations.

On physical examination she has a heart rate of 185 beats/min and a respiratory rate of 62 breaths/min. Her other vital signs are within age-appropriate limits. She had not been tachypneic on her previous visits. She appears fatigued, with a weak cry. She is tachypneic, with occasional grunting, but has good aeration and clear lung fields. Her cardiac examination findings are normal except for a capillary refill of 3 seconds. The remainder of her examination findings are within normal parameters. A diagnostic evaluation is commenced, and laboratory testing reveals the diagnosis.

DISCUSSION

Differential Diagnosis

The differential diagnosis for vomiting, tachypnea, tachycardia, and lethargy in infants should be broad. Infection should be among the first diagnoses considered in such patients. Gastroenteritis is the most common infectious cause of vomiting and dehydration leading to lethargy. Other gastrointestinal maladies, such as malrotation, volvulus, or even pyloric stenosis, should also be considered. Congestive heart failure should also be considered in patients with this presentation. Endocrine disorders, inborn errors of metabolism, and hydrocephalus or other neurologic pathology could also be considered.

AUTHOR DISCLOSURE Drs Otto, Orr, and Boyd have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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The Diagnosis

Laboratory evaluation included basic laboratory tests and a full sepsis evaluation, including blood, urine, and cerebrospinal fluid cultures. The complete blood cell count was normal. The basic metabolic panel showed a glucose level of 626 mg/dL (34.7 mmol/L), with a bicarbonate level less than 5 mEq/L (<5 mmol/L). The sodium level was 152 mEq/L (152 mmol/L), potassium level was 6.5 mEq/L (6.5 mmol/L), and chloride level was 123 mEq/L (123 mmol/L), with an anion gap greater than 24 mEq/L (>24 mmol/L). A whole blood ketone level was 3.6 mmol/L (normal, <0.6 mmol/L). A glycated hemoglobin level was performed and was 11.0%. Our patient was diagnosed as having diabetic ketoacidosis and was placed on a continuous insulin infusion.

The Condition

Neonatal diabetes mellitus (also known as congenital diabetes mellitus) is a rare disorder, occurring in approximately 1 of every 300,000 to 500,000 live births. In populations with significant consanguinity, neonatal diabetes mellitus has been reported in up to 1 in 21,000 births. Patients have impaired glucose sensing, leading to inappropriately low secretion of insulin in the setting of hyperglycemia. This is in contrast to type 1 diabetes mellitus, which is an autoimmune phenomenon wherein autoantibodies attack and destroy pancreatic β cells, leading to decreased production of insulin. Patients will present with a history of low birthweight, indicative of insulin's important role in utero in fetal growth. Persistent hyperglycemia causes excess diuresis, leading to failure to thrive and dehydration despite seemingly adequate intake. In addition to hyperglycemia and glucosuria, infants will often have biochemical features consistent with diabetes mellitus (ketonemia, ketonuria, elevated anion gap). A severe metabolic acidosis may lead to a compensatory hyperventilation, although the appearance of a tachypneic infant is often mistaken for respiratory infection despite absence of fever, cough, or wheezing. The time of presentation is variable, but the condition classically presents before 6 months of age, making autoimmune type 1 diabetes mellitus unlikely.

Neonatal diabetes mellitus is overwhelmingly a monogenic disorder, and molecular diagnostic testing is indicated for patients who present with clinical and biochemical evidence of diabetes mellitus before 6 months of age. The specific mutation can have a major effect on patients' clinical course and prognosis, with approximately 45% of patients with neonatal diabetes mellitus experiencing a transient course and 45% facing permanent diabetes. Those with transient neonatal diabetes will have remission after a treatment period of several months to a year, although relapse later in life occurs frequently. Disturbances of imprinted genes at chromosome 6q24 represent approximately 70% of transient neonatal diabetes, with far fewer transient cases due to adenosine triphosphate–regulated potassium channel mutations (*ABCC8* and *KCNJ11*). Permanent neonatal diabetes mellitus is due to a host of gene mutations involved in glucose sensing and the subsequent secretion of insulin. The most common mutations are in *KCNJ11* and *ABCC8*, genes encoding for K_{ATP} channels that regulate insulin secretion after sensing glucose. Patients require lifelong glycemic monitoring and treatment for diabetes mellitus. Our patient was later found to be a compound heterozygote for 2 presumed pathogenic variants in the *ABCC8* gene.

Management

The first therapeutic step is to begin to restore extracellular fluid volume, which has been depleted through osmotic diuresis and vomiting. Children with diabetic ketoacidosis are at risk for cerebral edema if rehydration is too rapid. Initial fluid resuscitation should begin with no more than 10 to 20 mL/kg of an isotonic solution (such as saline or lactated Ringers solution) over the first 1 to 2 hours. Remaining fluid deficits should be calculated and replaced over the next 48 hours. Insulin must be given to allow normal carbohydrate metabolism and to stop ketogenesis. Serum hyperosmolality should be normalized gradually and potassium monitored closely and replenished as needed. After acidosis control is accomplished, patients are transitioned to subcutaneous insulin therapy. Some patients with *KCNJ11* or *ABCC8* mutations may achieve glycemic control with oral sulfonylurea monotherapy, eliminating the need for insulin injections; thus, obtaining a molecular diagnosis is key in neonatal diabetes mellitus because results inform the clinical course and family counseling. However, not all mutations will respond to sulfonylurea therapy. Our patient underwent a trial of sulfonylureas, but the trial was deemed unsuccessful due to poor glycemic control and she was transitioned back to subcutaneous insulin therapy.

Lessons for the Clinician

- Neonatal diabetes mellitus, although rare, should always be on the differential diagnosis for infants with vomiting, lethargy, tachycardia, and tachypnea with absence of typical respiratory infection findings, such as wheezing, cough, rhinorrhea, or fevers.

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- A family history of consanguinity should raise suspicion for congenital disorders such as neonatal diabetes mellitus.
- Neonatal diabetes mellitus is characterized as transient or permanent, with approximately half of infants having a transient course resolving after weeks to months and half facing permanent diabetes mellitus.
- Although insulin is the first-line therapy in neonatal diabetes mellitus, infants should undergo a trial of oral sulfonylureas to identify patients who may be able to wean off insulin therapy.
- Molecular diagnosis is key to identify the specific mutation to help inform therapy and prognosis, as well as guide family counseling.

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Case 4: Vomiting and Tachypnea in a 9-week-old Girl

William R. Otto, Sarah Orr and Jennifer W. Boyd

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Acute Flaccid Myelitis in Children

Daniel R. Taylor, DO,* Sharyu Krishnakumar, MD*
**Department of Pediatrics, Saint Christopher's Hospital for Children, Philadelphia, PA*

AUTHOR DISCLOSURE Drs Taylor and Krishnakumar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product.

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An excerpt from *The Atlanta Journal-Constitution* in April 2019 describes a 3-year-old boy from the Atlanta area. "AC scoots around on his bottom in the living room of his Winder home as he plays with a toy train set. When it's time for school, his mother helps the 3-year-old into a black wheelchair with blue and green bars on the frame and a red Lego robot keychain attached to the headrest." The article goes on to explain that AC has had 4 surgeries and multiple infusions and may require potentially lifelong physical and occupational therapy. "This will never be over for us," his mother agonized in this article. AC was diagnosed earlier in the year as having acute flaccid myelitis (AFM).

Reminiscent of this 2019 article, several children living in small pockets of Brooklyn, New York, in the summer of 1916 awoke and were not able to move their arms and legs. Terrified parents rushed their children to local health centers, where physicians were perplexed by these symptoms, with many physicians having gone through their entire careers without ever seeing a case of what they soon recognized was paralytic poliomyelitis (polio). By December 1916, the polio epidemic had spread from New York City to more than 2 dozen states, spreading to the Midwest. Within 7 months there were 27,000 reported cases of polio, and 6,000 people had died, with thousands more paralyzed or having permanent limb deformities.

Fast forward 70 years to 1987, when doctors in the United States started reporting a few dozen cases of a severe respiratory illness tied to a virus that was first identified as enterovirus 68 (EV-68). Then, in 2008, a 5-year-old boy from New Hampshire contracted a febrile illness with neck pain, paralysis, and eventual death, which was attributed to EV-68. Tragic, but an isolated case, until 2014, when cases of what is now called AFM began to appear. AFM is considered a "poliomyelitis-like" syndrome with similar presentations as polio, which was eradicated in the United States in 1979 through an aggressive vaccine program.

Cases of AFM in the United States have demonstrated a biennial presentation, and most cases present in the summer and early fall. Whereas there were 120 reported cases of AFM in the United States in 2014, there were only 22 in 2015. An increase to 149 cases was noted in 2016, only to drop to 35 cases in 2017. The most recent data for 2018 include more than 220 cases, with this number continuing to rise as more children are reclassified as having AFM. Cases have been reported in 14 countries, including Norway, Canada, France, and Great Britain, but the United States is the epicenter. The alternating-year pattern of this disease continues to be a mystery.

Eighty percent of cases present with typical prodromal symptoms of an upper respiratory tract infection or gastrointestinal illness and fever, a typical presentation for dozens of common childhood illnesses. Yet, a median of 5 days evolves before the presentation of neurologic symptoms such as onset of limb weakness or paralysis, hypotonia, hyporeflexia or areflexia, facial droop or

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weakness, ophthalmoplegia affecting the ocular muscles or eyelids, and dysphagia or swallowing dysfunction. Paralysis is rapid (hours to days) and is typically asymmetrical with any combination of limb involvement but with a preference for the upper extremities. The pattern of weakness of AFM points to a lower motor neuron disease process, which is similar to entities such as polio, Guillain-Barre syndrome, amyotrophic lateral sclerosis, and botulism. Cranial nerve dysfunction is seen in approximately 30% of patients.

Although the cause of AFM is still not known, EV-68 is suspected to play a role because this virus has been detected in 47% of respiratory specimens of confirmed cases of AFM when collection has occurred within the first 2 weeks after the onset of symptoms. No other candidate pathogen has been consistently detected in cases of AFM.

The hypothesized pathogenesis of EV-68 playing a role in AFM is a newly enhanced neurotropism of EV-68 with greater potential to infect and destroy neurons. This mechanism has also been demonstrated in laboratory mice infected with recent EV-68 strains.

The average age at presentation of AFM is 4 years; the oldest confirmed case was a 32-year-old man, and the youngest less than 1 year old. Ninety percent of cases occur in children, with most aged 3 to 6 years.

In June 2015 the Council of State and Territorial Epidemiologists approved a standardized definition for AFM used by the Centers for Disease Control and Prevention (CDC) that classifies patients under investigation for AFM as probable or confirmed cases.

The clinical criterion for AFM is an illness with acute onset of flaccid limb weakness. Imaging criterion that supports the diagnosis of AFM is magnetic resonance imaging (MRI) of the spinal cord showing lesions in the gray matter spanning 1 or more vertebral segments. Supportive laboratory results include cerebrospinal fluid pleocytosis (white blood cell count $>5/\mu L$ [$>0.005 \times 10^9/L$]).

Confirmed cases, as designated by the CDC, include clinically compatible criteria of AFM along with the classic MRI findings. Probable cases are defined as clinically compatible criteria with a normal MRI but with a cerebrospinal fluid pleocytosis.

To date there is no standard of care for treatment, which has included corticosteroids, antivirals, intravenous immunoglobulin, and exchange transfusions. Hence, early involvement of a neurologist with expertise in AFM is warranted. Children who are affected may need months if not years of physical and occupational therapy and tendon or nerve transfer surgeries to strengthen their weakened muscles and to regain their ability to eat. Recovery, tragically, is often incomplete, with most children having motor deficits and muscular atrophy more than a year after onset of symptoms.

At the present time, the CDC, along with experts in the field, has published interim considerations based on the available evidence (https://www.cdc.gov/acute-flaccid-myelitis/hcp/clinical-management.html). "There is no indication that any specific targeted therapy or intervention should be either preferred or avoided in the treatment of AFM. There are currently no targeted therapies/interventions with enough evidence to endorse or discourage their use for the treatment or management of AFM." The CDC suggests early expedited consultation with neurology and infectious disease experts and reporting of all probable cases to the CDC. Recommendations for testing are published on the CDC website: [https://www.cdc.gov/acute-flaccid-myelitis/diagnosis.html]. The establishment of real-time EV-68 surveillance networks is vital to isolate early outbreaks geographically. There needs to be more outreach to physicians and other health-care providers, including the public, to detect, test, and treat AFM at its earliest onset to attempt to mitigate the worse-case outcomes. Utilization of best practices, networks of care, and advanced technologies in virology and pharmacokinetics are necessary to try to achieve the best outcomes for patients with AFM.

This novel, acute, and, so far, mysterious disorder reminds us once again that nature is constantly evolving along with the pathogens that infect, interact with, and coexist with the human species. This disease is humbling a medical community that is racing to develop improved diagnostic criteria for AFM and to develop standards of care for the hundreds of children who have been affected and will continue to be affected in the future. The medical community must pursue research into the pathogenesis and must study best practices in physical rehabilitation and nerve transfer surgery to maximize outcomes and, if EV-68 is definitively identified as the pathogen, to develop appropriate vaccines. Time is of the essence.

COMMENT: The appearance of a new disease that initially presents with very common symptoms and progresses in a small subset of patients to significant morbidity results in heightened concerns and fears for children, parents, and medical providers alike. This *In Brief* reminds me of questions that a mentor of mine, Dr Barton Childs, an internationally

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renowned geneticist, would always ask us to consider when evaluating patients: "Why this child, why this disease, and why now?" These wise questions seem so poignant when contemplating AFM. A common viral illness (suspected to be an enterovirus but not yet proved) infects many children, yet, fortunately, only a small proportion go on to develop AFM. Of those diagnosed, the morbidity spans wide variability, from weakness in a single limb to paralysis of all extremities. AFM has reminded our medical community of the lessons learned from polio, when education of primary care providers was essential for early recognition and the development of a vaccine resulted in eradication of the disease in the United States. The CDC issued a warning on July 9, 2019, urging providers to consider the diagnosis of AFM as early as possible, to contact local health departments, and to obtain specimens of serum, cerebrospinal fluid, stool, and nasopharyngeal swabs in addition to MRI testing. National and international coordination of efforts is needed to best understand the epidemiology, coordinate multicenter studies to identify best therapies, and develop an animal model for possible vaccine development. In the meantime, the Transverse Myelitis Association has created an around-the-clock support portal for physician consultation when AFM is being considered as the diagnosis. The portal address is https://mvelitis.org/living-with-mvelitis/resources/afm-physician-support-portal/. Although many, many questions remain concerning AFM, the past track record of coordinated medical research provides me with hope that, just as with polio, best practices will be developed and, optimally, prevention through vaccines can be achieved.

– Janet Serwint, MD
Associate Editor, *In Brief*

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Acute Flaccid Myelitis in Children

Daniel R. Taylor and Sharyu Krishnakumar

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in Brief

Pulse Oximetry

Viviane G. Nasr, MD,* James A. DiNardo, MD*
**Department of Anesthesiology, Critical Care, and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA*

Pulse oximetry provides a readily available, easy-to-use, noninvasive method for measurement of pulse oxygen saturation (Spo_2) that can be obtained by placement of a small probe on the finger, toe, or ear lobe of a patient. In neonates and infants, probes may also be placed on the palms, feet, arms, cheeks, tongue, penis, nose, or nasal septum. Small, portable pulse oximetry probes can be applied to patients of any size, from premature neonates to the largest adults, in virtually any setting, from outpatient offices and hospital settings to mountaineering expeditions. The first practical pulse oximeter became commercially available in 1983. Obtaining Spo_2 measurements is now so simple that it is commonly referred to as the "fifth" vital sign.

The basic technology behind pulse oximetry is the photoplethysmographic (PPG) waveform. The PPG waveform is an amplified and highly filtered measurement of light absorption by local tissue over time. At a minimum, all modern pulse oximeters extract and display SpO_2 and heart rate from the PPG waveform every 3 to 6 seconds; some display the PPG waveform as well. One side of the pulse oximeter probe contains 2 light-emitting diodes that transmit 2 wavelengths of light, and the other side contains a photodetector. Red light at 660 nm and near-infrared (NIR) light at 940 nm is transmitted through intervening tissue (skin, arteries, capillaries, veins, bone, and fat), with the light not absorbed in this pathway detected by the photodetector on the opposite side. Examples of small, portable and disposable, elasticized pulse oximeter probes are shown in Fig 1.

The key concept behind pulse oximetry, the technology to determine the hemoglobin saturation of pulsatile arterial blood, was elucidated by the Japanese electrical engineer Takuo Aoyagi in the 1970s. Oxyhemoglobin absorbs substantially more NIR than red light, and, conversely, deoxyhemoglobin absorbs substantially more red than NIR light. Thus, the ratio (R) of absorption amplitudes of red light to NIR light in the light path can be used to calculate SpO_2 given the known red and NIR light absorption patterns of oxyhemoglobin and deoxyhemoglobin. The actual light path through arteries and veins has a pulsatile alternating current (AC) and a nonpulsatile direct current (DC) component (Fig 2). R (also known as the Red:NIR modulation ratio or double ratio) is determined by the microprocessor of the pulse oximetry device using the following formula: $(A_{\text{red, AC}} / A_{\text{red, DC}}) / (A_{\text{IR, AC}} / A_{\text{IR, DC}})$, where $A =$ absorption amplitude. Using a calibration curve, the microprocessor then converts R to the hemoglobin saturation of arterial blood (Spo_2) that is displayed on the monitor screen. The calibration curve is empirically generated by measuring R in healthy volunteers whose saturations were altered from 100% to approximately 70%.

The PPG waveform as displayed on a monitor is the NIR output inverted so that it appears in the same orientation as an arterial pulse. The raw waveform is filtered such that it is constantly being smoothed and having its size adjusted. The PPG waveforms can provide valuable information regarding the patient's perfusion

AUTHOR DISCLOSURE Drs Nasr and DiNardo have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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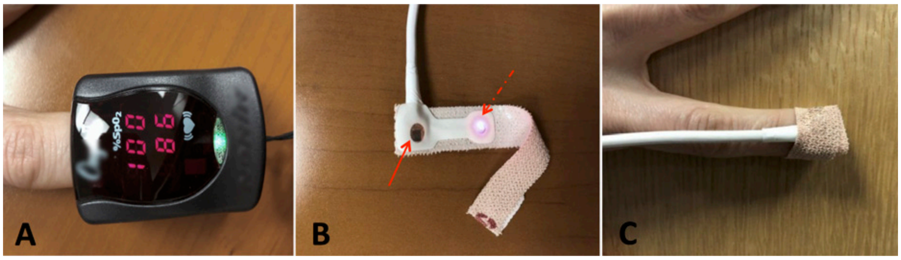

Figure 1. A. A small, portable pulse oximeter probe suitable for use on the finger or toe of a child or adult. The probe displays pulse oxygen saturation and heart rate. B. A disposable, elasticized pulse oximeter probe suitable for use on a neonate or infant. The probe is attached by the cable to a monitor. The 2 light-emitting diodes (red dashed arrow) and the photodetector (red arrow) are visible. C. Finger application of a disposable probe. The probe can also be applied to toes or across the hand or foot in neonates.

and cardiac rhythm and can aid in the diagnosis of cardiovascular abnormalities. Alterations in cardiac rhythm resulting in an irregular perfusion pattern are easily appreciated on the PPG waveform, as is pulse pressure variation induced by pericardial tamponade or hypovolemia.

Pulse oximeters approved by the Food and Drug Administration (FDA) must be accurate to root mean square error of less than 3% at saturations between 70% and 100%. However, external and patient factors can affect the performance of pulse oximeters (Table). In addition, altitude affects the partial pressure of oxygen, leading to lower arterial saturations. A normal Spo$_2$ at high altitude is 95%. At saturations lower than 85%, the measurements are not considered accurate.

Pulse oximetry is a valuable monitoring tool in any clinical situation associated with hypoxemia. As such, changes in Spo$_2$ are a sensitive indicator of disease severity and response to treatment in conditions associated with ventilation/perfusion mismatch and intrapulmonary or intracardiac shunt, such as asthma, bronchopulmonary dysplasia, bronchiolitis, pneumonia, and congenital heart disease. To the contrary, conditions associated with hypercarbia due to reduced alveolar ventilation (hypoventilation) as a result of partial airway obstruction or depression of ventilation will not be associated with significant changes in Spo$_2$, particularly if supplemental oxygen is administered, until partial pressure of carbon dioxide in arterial blood is

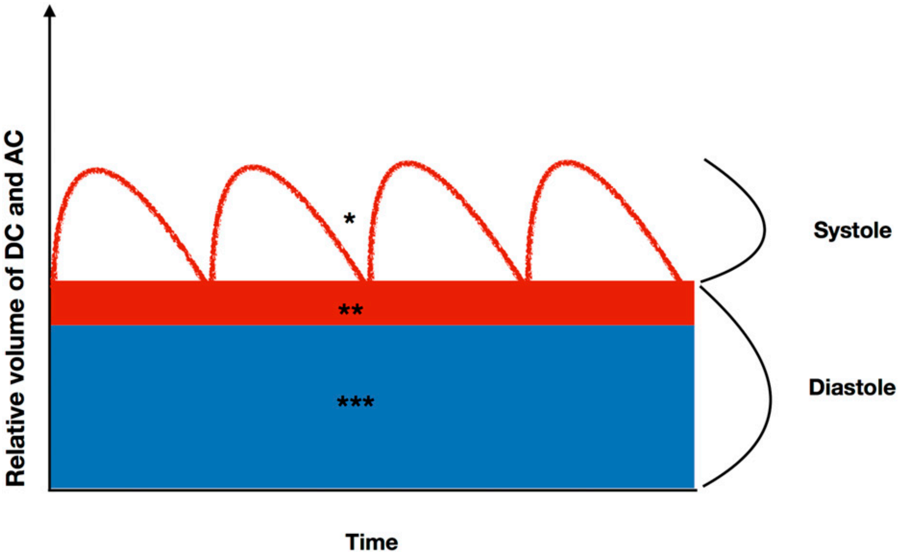

Figure 2. Photoplethysmographic measurement in each wavelength enables assessment of the contribution of arterial blood to the total absorption of light because the photoplethysmographic signal amplitude reflects changes in arterial blood volume. The pulsatile alternating current (AC) of the arteries is denoted by *; the nonpulsatile direct current (DC) of the arteries is denoted by **; and the DC of the venous and capillary blood and that of the tissues is denoted by ***. The ratio AC/DC allows each pulsatile component (AC) to be normalized for its nonpulsatile baseline (DC). The DC volume includes the tissues and blood in the veins, the capillaries, and the nonpulsatile component of the arteries (diastole). Consequently, the AC volume includes only the pulsatile, systolic component of the arteries.

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TABLE. Factors Leading to Low or Inaccurate Pulse Oxygen Saturation (Spo$_2$) Readings

LOW Spo$_2$ READING	INACCURATE Spo$_2$ READING
Poor perfusion (low cardiac output, shock, hypothermia, vasoconstriction)	Motion artifact
Skin pigmentation	Irregular cardiac rhythms
Nail polish (dark, blue, green)	Electromagnetic interference
Probe position	Carboxyhemoglobin
Ambient light interference	Methemoglobin
Intravenous dyes (methylene blue, indocyanine green, and indigo carmine)	
Venous pulsations (right heart failure, adhesive probe too tight)	

extremely elevated. Hence, use of pulse oximetry could result in a delay of diagnosis in these conditions.

Spo$_2$ monitoring has been effectively used as a screening tool for the detection of critical congenital heart disease (CCHD) because most patients with CCHD present with hypoxemia that does not produce visible cyanosis and, therefore, is not detectable clinically. Pulse oximetry has high specificity (99.9%; 95% confidence interval [CI], 99.7%–99.9%) of screening at or after 24 hours, and false-positives are uncommon (approximately 0.05%).

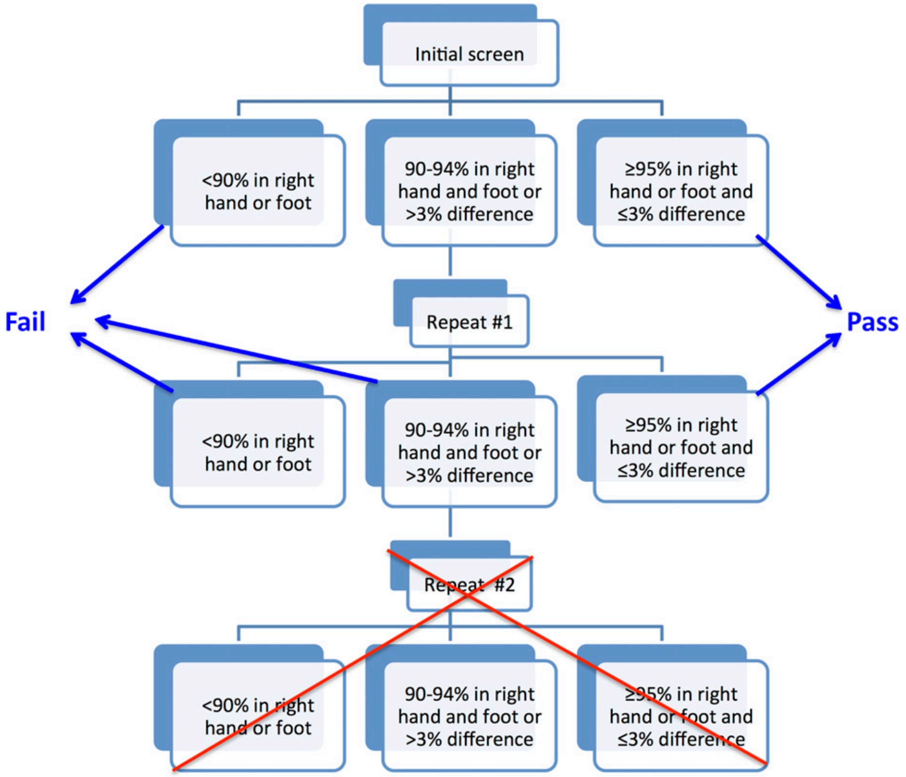
Initial screen
<90% in right hand or foot
90-94% in right hand and foot or >3% difference
≥95% in right hand or foot and ≤3% difference
Fail
Repeat #1
Pass
<90% in right hand or foot
90-94% in right hand and foot or >3% difference
≥95% in right hand or foot and ≤3% difference
Repeat #2
<90% in right hand or foot
90-94% in right hand and foot or >3% difference
≥95% in right hand or foot and ≤3% difference

Figure 3. Currently proposed screening protocol using pulse oxygen saturation to diagnose critical congenital heart disease.

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The sensitivity of screening to detect CCHD is estimated to be 78%, but it may range from 36% to 92% depending on the particular cardiac lesion. Targeted lesions screened by pulse oximetry include single-ventricle physiology (hypoplastic left heart syndrome, tricuspid atresia, pulmonary atresia), tetralogy of Fallot, transposition of the great arteries, interrupted aortic arch, and truncus arteriosus.

In 2011, pulse oximetry was introduced into the US Uniform Screening Panel for Newborns and became mandatory in 8 states in 2013. States that have implemented mandatory screening have decreased infant cardiac deaths by 33.4% (95% CI, 10.6%–50.3%), with an absolute decline of 3.9% (95% CI, 3.6%–4.1%) in deaths per 100,000 births compared with states with nonmandatory screening. Currently, 36 states and the District of Columbia have laws requiring newborn screening of CCHD and 12 states have regulations or guidance on newborn screening. Similarly, the Canadian Cardiovascular Society, along with the Canadian Pediatric Cardiology Association, has recommended the use of pulse oximetry as a screening tool in addition to other modalities to improve the detection of CCHD and has recommended that it should be performed between 24 and 36 hours of age. A recent modification of the screening algorithm with 1 repeated screening instead of 2 has been proposed and may potentially improve detection of hypoxemic disease in neonates without significant effect on CCHD detection false-positive rates. Figure 3 is an illustration of the modified algorithm.

Pulse oximetry, the “fifth” vital sign, is a simple, noninvasive, inexpensive method to continuously monitor Spo_2. When coupled with display of the PPG waveform it also provides valuable information on perfusion and cardiac rhythm and can aid in the diagnosis of cardiovascular abnormalities.

COMMENT: Pulse oximetry has become a great tool to aid clinicians in detecting hypoxia in a noninvasive manner. The fact that it can be used in situations outside the health-care facility, such as mountaineering expeditions, demonstrates its ease of use and portability. It is essential for pediatricians and health-care providers to understand the factors that can affect the accuracy of pulse oximetry readings to ensure the safest care of our patients. Although pulse oximetry is an important technological aid, as with any technology, clinical correlation is essential to consider. One of the Choose Wisely concepts published by the Society of Hospital Medicine suggests not using continuous pulse oximetry routinely for children with acute respiratory illness unless they are on oxygen. Complete reliance on pulse oximetry without considering the clinical findings can lead to prolonged hospitalizations or can raise concerns regarding monitor fatigue if the monitor keeps alarming due to probe malfunction or motion artifact. Conversely, if a pulse oximetry reading is reassuring but does not fit the clinical scenario, further information can be obtained through a blood gas measurement. The use of pulse oximetry serves as an example of the importance of considering the available technological results from testing with the physical examination of the patient when making clinical decisions.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

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Bronchiolitis: 1. A; 2. D; 3. B; 4. C; 5. C.
Acne Vulgaris in the Pediatric Patient: 1. A; 2. B; 3. A; 4. A; 5. E.

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Pulse Oximetry

Viviane G. Nasr and James A. DiNardo

Pediatrics in Review 2019;40;605

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Visual Diagnosis

Button versus Battery: Foreign Body Ingestions in Pediatrics

Joran Clute, MD,* Teresa Frey, DO,[†] Jennifer Reed, MD, FAAP[†]

*Department of Anesthesiology, University of Iowa Hospitals and Clinics, Iowa City, IA
[†]Department of Pediatrics, University of South Dakota Sanford School of Medicine, Sanford Children's Hospital, Sioux Falls, SD

PRESENTATION

A 3-year-old girl is brought to the emergency department by her mother with a 1 hour history of sudden-onset abdominal pain and drooling. The child frequently places objects in her mouth, and her mother believes that she has swallowed a coin, although the event was unwitnessed. Her pain occurred intermittently before presentation.

On physical examination she is in no acute distress. Her abdominal examination is significant for epigastric tenderness. Her vital signs are as follows: pulse, 100 beats/min; respiratory rate, 26 breaths/min; and blood pressure, 109/56 mm Hg.

An anteroposterior abdominal radiograph (Fig 1) shows a radiopaque 2.5-cm round object in the distal esophagus; the appearance is consistent with a coin.

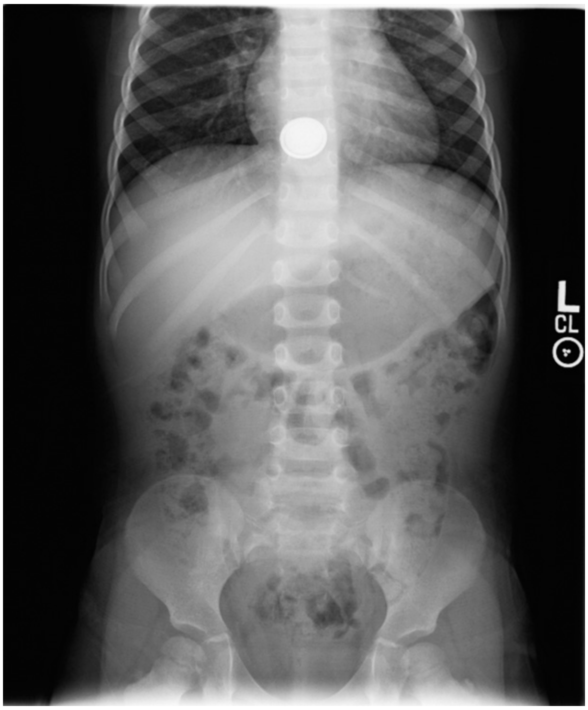

Figure 1. Abdominal radiograph significant for a 2.5-cm round radiopaque foreign body with a double rim in the distal esophagus.

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After the initial radiograph she vomits twice; both pain and drooling resolve. She is transferred by private vehicle to an outside hospital for an esophageal foreign body removal by endoscopy (esophagogastroduodenoscopy). On arrival, a repeated abdominal radiograph is normal, with no foreign body visible. An oral challenge in the emergency department results in severe abdominal pain.

More careful review of the original radiograph reveals the object to have a halo effect, consistent with a button battery. An endoscopy is performed, which confirms the diagnosis.

DIAGNOSIS

Endoscopy reveals a 3-cm area of patchy superficial ulceration and 2 deeper linear ulcerations without obvious areas of perforation that were caused by the battery lodging in her esophagus (Fig 2).

DISCUSSION

Although button batteries can become lodged in multiple segments of the gastrointestinal tract, the esophagus is the most vulnerable. When button batteries become lodged in the esophagus they cause damage by 3 mechanisms. First, they exert physical pressure on the esophageal tissues. Second, they generate an electrolytic current that hydrolyzes surrounding fluids as the circuit from the cathode (positive) to the anode (negative) is completed in the tissue. (1) Last, they leak alkaline battery contents into the surrounding environment. (1)

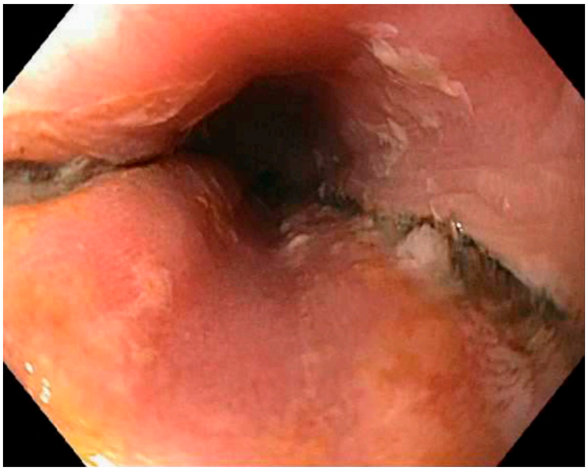

Figure 2. Endoscopic image significant for a 3-cm area of patchy superficial ulceration and 2 deeper ulcerations without obvious areas of perforation.

Burns and life-threatening complications can occur within 2 hours of ingestion. (1) From 1985 to 2016, the percentage of cases resulting in moderate to severe outcomes or death has gone from 0.4% to 3.3% as reported by the National Capital Poison Center. (1) The increase in these outcomes corresponds to an increase in household use of 20-mm lithium coin cells. (2) These lithium coin cells generate more external current and harmful hydroxide than other button batteries, leading to worse outcomes after an ingestion. (2)

The most recent data from the National Capital Poison Center show that there were 2,144 button battery ingestions in children younger than 6 years in 2016. (1) If foreign body ingestion is suspected, an anteroposterior abdominal radiograph should be carefully examined for a circular radiopaque object with an outer peripheral rim, commonly known as the *double-rim* or *halo effect*. On the lateral view, the different sizes of the anode and cathode create a "step-off." These diagnostic features are crucial to early identification and treatment (Table). (3)

There are many potential complications from button battery ingestion, including tracheal stenosis, esophageal stricture, tracheoesophageal fistula, esophageal perforation, mediastinitis, vocal cord paralysis, aspiration pneumonia, empyema, lung abscess, pneumothorax, spondylodiscitis, or death from exsanguination secondary to perforation of the aorta. (1) These complications can often be delayed up to 9 days for tracheoesophageal fistulas, weeks for recurrent laryngeal nerve injury, 28 days for esophageal-vascular fistulas, and weeks to months for esophageal strictures or spondylodiscitis. (1)

The most important factor in management is the prompt removal of the button battery, optimally within the first 2 hours. (1)(2) Endoscopic removal is necessary for visualization of the injury and to allow for anticipation of injury progression. (1)(2) Also, recent data showed benefit from irrigation and suction of injured areas with 50 to 150 mL of 0.25% sterile acetic acid in patients without evidence of perforation. (4) If there is an injury to the esophagus the patient should be admitted to the hospital and observed for any of the previously mentioned complications. If there is concern about the development of a fistula, the patient should be monitored with serial imaging and fecal occult blood testing. (1) Serial imaging can include either contrast computed tomography or magnetic resonance imaging. (1) An esophagram using water-soluble contrast should be performed 1 to 2 days after removal. (1) A clear liquid diet can be initiated if the patient is stable and the esophagram is normal. (1) The diet can be advanced to soft foods as tolerated, and the patient

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TABLE. **Appearance and Treatment of Coin versus Button Battery Ingestions**

	COIN	BATTERY
Appearance in the trachea on the anteroposterior radiograph	Line or narrow oval	Line or narrow oval
Appearance in the trachea on the lateral radiograph	Circle	Circle with double rim or halo
Appearance in the esophagus on the anteroposterior radiograph	Circle	Circle with double rim or halo
Appearance in the esophagus on the lateral radiograph	Line or narrow oval	Line or narrow oval; "step-off" seen at edge between anode and cathode
Treatment based on location	Esophagus: remove immediately Stomach: observation	Esophagus: emergency removal Stomach: observation if asymptomatic; remove with endoscopy if symptoms such as vomiting or pain

should remain on soft foods for 28 days. (1) A repeated esophagram 4 weeks after removal can be useful to evaluate for delayed complications, specifically an esophageal stricture; if normal, follow-up is unnecessary unless the patient develops symptoms. (5)

PATIENT COURSE

An esophagram on day 2 of hospitalization had no evidence of perforation or fissure, and a computed tomography angiogram of the chest on day 4 of hospitalization revealed no abnormal air or fluid collections along the esophagus. The button battery was never recovered or seen on imaging studies after the initial abdominal radiograph. It is suspected that the battery was lodged in the esophagus for 2 to 4 hours and expelled during the episodes of emesis after the initial evaluation. Ultimately, she was discharged without complications.

A second esophagogastroduodenoscopy 11 days after the ingestion showed slight mucosal irregularity at the site of the previous battery ingestion. The ulcerations resolved, and there were no visualized strictures. A follow-up esophagram 5 weeks after ingestion was normal, with no concern for stricture. At that visit, the patient was asymptomatic, and she had resumed eating normally, with no abdominal pain or vomiting.

Summary

- Button battery ingestions are becoming more prevalent, and popular 20-mm lithium coin cells are associated with adverse outcomes. (2)
- It is important for all clinicians to be able to recognize symptoms of a foreign body ingestion, radiographically identify button batteries, and promptly remove, treat, and monitor the patient.

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Visual Diagnosis: Button versus Battery: Foreign Body Ingestions in Pediatrics

Joran Clute, Teresa Frey and Jennifer Reed

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Dysmorphology

Alexander Youngjoon Kim, MD,* Joann Norma Bodurtha, MD, MPH*[†]

*Department of Genetic Medicine, [†]Departments of Pediatrics and Oncology, Johns Hopkins University School of Medicine, Baltimore, MD

Education Gaps

1. Children and families affected by genetic conditions frequently experience protracted diagnostic odysseys requiring the use of complex esoteric tests.
2. A recent survey of the American Academy of Pediatrics membership revealed that pediatricians are aware of the importance of genetic medicine. However, it also revealed that medical training has not prepared most of them to direct genetic evaluations and order genetic testing.
3. Referrals to genetic subspecialists for evaluation, counseling, and testing can be challenging for patients and their families.
4. The rapid evolution of genetic medicine, including the number of known genetic conditions and the availability of diagnostic testing methods, necessitates ongoing education.

Objectives

After completing this article, readers should be able to:

1. Recognize a distinctive pattern of dysmorphic features concerning for a genetic condition.
2. Construct a genetic differential diagnosis through the use of resources such as the Online Mendelian Inheritance in Man® database and literature review.
3. Appreciate the complexities of genetic testing and discussing the results.
4. Demonstrate familiarity with the clinical findings of CHARGE syndrome, Cowden syndrome, and Loeys-Dietz syndrome.
5. Appreciate the importance of newborn screening and the availability of resources such as ACTion sheets and confirmatory algorithms for pediatricians.

AUTHOR DISCLOSURE Drs Kim and Bodurtha have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CHARGE	coloboma, heart defect, choanal atresia, restricted growth, genitourinary anomaly, ear anomaly
OMIM	Online Mendelian Inheritance in Man
POSSUM	Pictures of Standard Syndromes and Undiagnosed Malformations

INTRODUCTION

It is time to stop thinking of genetic medicine as only applicable to a small set of rare diseases affecting a limited cohort of patients. Although individual genetic diagnoses are rare, their aggregate effect on human health is not. An estimated 8% of

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live births are affected by a Mendelian condition, which is associated with variation in a single gene, and/or a congenital anomaly. (1) In addition, the molecular basis is now known for more than 6,500 Mendelian conditions, genetic susceptibilities, and other phenotypes. (2) As this number continues to increase, so will the challenges facing clinicians tasked with integrating genetic medicine into the individualized care of their patients. It is impossible to know the epidemiology, pathogenesis, clinical aspects, management, and prognosis for all known genetic conditions. And even when a clinician knows everything there is to know about a specific genetic condition, this knowledge may be inadequate if the evidence base is limited by the genetic condition's relative rarity and/or recent discovery.

As a group, pediatricians have long recognized the importance of genetic medicine, including use of the family history to inform patient care. We also recognize the limitations of our training and time for incorporating genetic evaluation and management principles into routine clinical practice. For example, a recent survey of the American Academy of Pediatrics membership revealed that 53.1% of respondents identified inadequate training and/or practice guidelines for genetic test selection, 60.2% regarding genetic test interpretation, and 57.4% regarding ongoing genetic management. Furthermore, 48.9% identified inadequate time for genetic test interpretation. These concerns cannot be addressed with referrals alone. (3) The referral process is often complicated by long wait times and travel distances, which are likely exacerbated by the continued scarcity of genetic subspecialists. (4)(5)

Despite these difficulties, incorporating genetic medicine into the standard of care has the potential to revolutionize and individualize patient care. Overcoming current barriers will likely necessitate ongoing education and innovative approaches that cross medical subspecialty and geographic boundaries. For example, the American College of Medical Genetics and Genomics ACTion Sheets and Confirmatory Algorithms (http://www.ncbi.nlm.nih.gov/books/NBK55827/) are available to pediatricians who have received abnormal newborn screen results concerning for an inborn error of metabolism, free of charge. (6) Additional resources that may be available in the future include telemedicine programs and other technology-enabled systems.

But for now, what should a pediatrician do when encountering a distinctive-appearing child with dysmorphic features?

PATIENT 1

You are performing the admission history and physical examination for a previously healthy 7-year-old boy with a working diagnosis of community-acquired pneumonia. His respiratory rate is 55 breaths/min on nasal cannula. The remainder of his physical examination seems normal at first. You then notice penile freckling.

PATIENT 2

You are evaluating a 2-week-old girl, born at term, for her first well-baby check. She has been feeding, voiding, and stooling well. Her physical examination is mostly reassuring. She is pink and vigorous. You then notice widely spaced eyes, increased joint laxity, and a bifid uvula (Fig 1).

DYSMORPHOLOGY

Dysmorphology was first described by David W. Smith in 1966 as the "study of, or general subject of, abnormal development of tissue form." His intention for defining it in this manner was to encourage an approach that did not presume an environmental cause, as is the case with teratology. (7) Since then, dysmorphology has evolved into a discipline that addresses the variation of physical features with increasing precision. The Elements of Morphology (https://elementsofmorphology.nih.gov) is a resource that delineates the standardized nomenclature for the description of physical features, and it is available free of charge. (8) The importance of clearly defined and consistent terminology is easily demonstrated. Describing an ear as abnormal is neither significant nor specific. A detailed description can be both. For example, a short and wide ear with a cuplike overall configuration, triangular concha, and discontinuous antihelix and antitragus is suggestive of CHARGE syndrome. The acronym

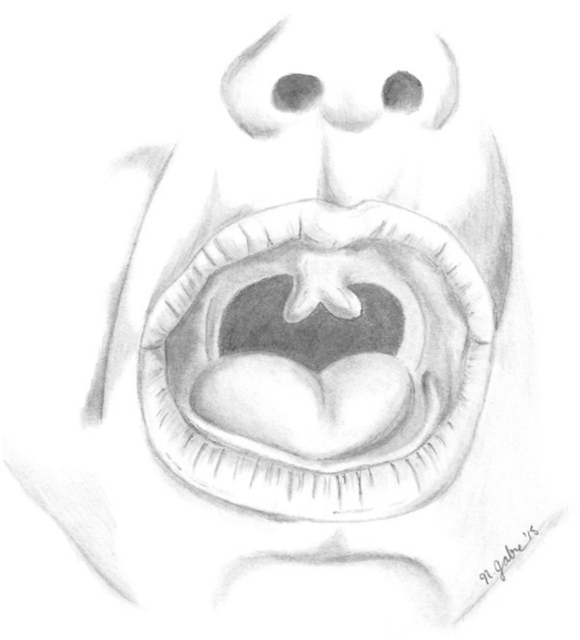

Figure 1. Example of a bifid uvula.

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CHARGE represents the clinical findings that are classically described with this genetic condition: coloboma, heart defect, choanal atresia, restricted growth, genitourinary anomaly, and ear anomaly (Fig 2). If there is specific concern for CHARGE syndrome, then *CHD7* gene testing can be performed to confirm the diagnosis. (9)(10) In this illustrative scenario, genetic dysmorphology has been used to describe an observable physical feature, recognize this feature as suggestive of a specific diagnosis, and answer the question "Is this genetic?" In practice, a genetic evaluation requires systematic consideration of the family history, clinical findings, identifiable patterns, differential diagnoses, and optimal genetic testing strategy.

Understanding a patient's family history is fundamental to dysmorphology because the family history informs the baseline likelihoods of specific genetic diagnoses for specific clinical findings. Taking a family history is useful, regardless of whether it is considered positive or negative. A family history can be considered positive if it fulfills the Rule of Two/Too described by Robert A. Saul. This includes 2 or more affected family members, 2 or more affected generations, too many clinical findings, and too early age at onset. (11) When the family history is visually represented in the form of a pedigree, there may be a recognizable inheritance pattern (Table 1). A positive family history is suggestive of an inherited genetic trait and can facilitate a focused genetic evaluation. For example, a young girl with mucocutaneous melanocytic macules can be diagnosed as having Peutz-Jeghers syndrome if her father is known to be affected. (12) In contrast, an ostensibly negative family history does not exclude the possibility of an inherited genetic trait. For example, a common theme of the earlier studies describing Alagille syndrome was the subsequent diagnosis of seemingly unaffected parents. (13) Furthermore, a negative family history may actually be positive if the inheritance pattern is not as obvious as the autosomal dominant pattern. These include autosomal recessive, both the typical male-predominant and the atypical female-predominant X-linked, and matrilineal mitochondrial patterns. (14)(15) Ultimately, even the absence of a positive family history is informative because it suggests against the possibility of a genetic diagnosis that is expected to be familial in a significant percentage of cases.

As demonstrated by the example of the "abnormal" ear suggestive of CHARGE syndrome, differences in observable physical features can be suggestive of specific genetic etiologies. However, not all anomalies are specific and/or significant, and there are a few different types to consider (Table 2). A malformation is a "morphologic defect of an organ, part of an organ, or a larger region of the body resulting from an intrinsically abnormal developmental process". (16) A disruption is a "morphological defect of an organ, part of an organ, or a larger region of the body

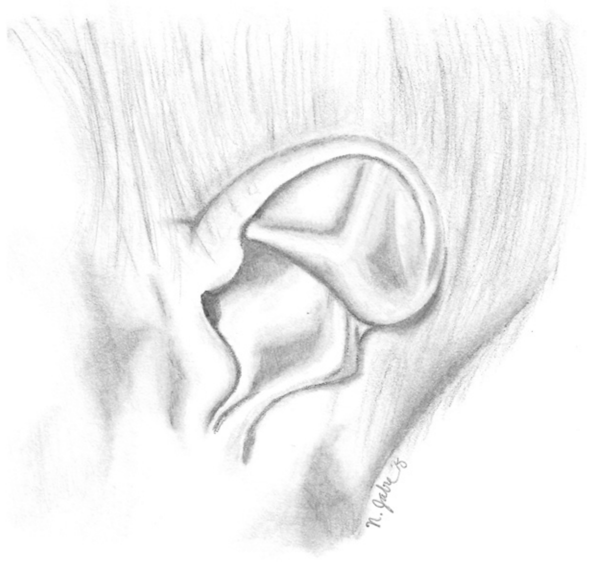

Figure 2. Example of a CHARGE ear.

TABLE 1. **Examples of Recognizable Inheritance Patterns**

Autosomal dominant
Typically has multiple affected individuals in a single generation
Typically has similar manifestations and severity in females and males
Typically has multiple generations involved, without "skipping" of generations
Autosomal recessive
Typically has multiple affected individuals in a single generation
Typically has similar manifestations and severity in females and males
When multiple generations are involved, typically has "skipping" of generations
X-linked
Typically has multiple affected individuals in a single generation
Typically has more manifestations with higher severity in males than in females
When multiple generations are involved, never has father-to-son transmission
Mitochondrial
Typically has multiple affected individuals in a single generation
Manifestations and/or severity are not typically dependent on biological sex, can be variable
When multiple generations are involved, always has mother-to-child transmission

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resulting from the extrinsic breakdown of, or an interference with, an originally normal developmental process". (16) A deformation is an "abnormal form, shape, or position of a part of the body caused by mechanical forces". (16) A dysplasia is an "abnormal organization of cells into tissue(s) and its morphologic result(s)". (16) If an observed anomaly can be conceptualized as a malformation or a dysplasia, then a genetic etiology can be considered more likely. In contrast, if an anomaly can be conceptualized as a disruption or a deformation, then an environmental etiology can be considered more likely. Anomalies can also vary in significance. Those that are expected to affect a patient's health can be considered major anomalies. Those that are not expected to affect a patient's health can be considered minor anomalies.

Observable physical features can vary in number, size, placement, and shape. For example, an ear can be missing, measure less than the third percentile for age, be borderline low-set, have a squared superior portion of the helix, etc. It can be helpful to quantify objective differences, which are typically more important than subjective ones. The *Handbook of Physical Measurements* and *Smith's Recognizable Patterns of Human Malformation* are references that can be used to learn how to measure a body part and then compare this measurement with published standards. (17)(18) Any differences in a child's overall growth and development are important clues to consider as well. It can be challenging to determine the significance of anomalies beyond any major or minor medical implications. For example, polydactyly is a common anomaly that can be observed in isolation and in the context of more than 300 genetic syndromes. (19) The significance of this finding is determined by its specific characteristics and by the contexts of family- and population-level variability. Type B postaxial polydactyly, which consists of a rudimentary sixth digit arising from the ulnar/fibular aspect of the fifth digit, has been observed at a frequency approaching 1 in 100 in specific ethnic populations and 1 in 3,000 in others. (20) Predictably, this form of polydactyly is typically expected to be an isolated finding but to differing degrees depending on ethnicity.

TABLE 2. **Examples of Anomaly Types**

Malformation
Morphologic defect of an organ, part of an organ, or a larger region of the body resulting from an intrinsically abnormal developmental process.
Example: atrioventricular septal defect (ie, failure of the endocardial cushions to form the atrial and ventricular septa)
Disruption
Morphologic defect of an organ, part of an organ, or a larger region of the body resulting from the extrinsic breakdown of, or an interference with, an originally normal developmental process.
Example: amniotic bands (ie, minor to major disfigurement and/or amputation affecting a single body part or multiple body parts)
Deformation
Abnormal form, shape, or position of a part of the body caused by mechanical forces.
Example: Potter facies (ie, combination of flattened facial profile and nose, epicanthal and infraorbital folds, low-set ears, and recessed chin)
Dysplasia
Abnormal organization of cells into tissue(s) and its morphologic result(s).
Example: thanatophoric dysplasia (ie, severe genetic condition affecting the development of the axial and appendicular skeleton, often but not always lethal)

It is also important to consider anomalies in the context of others and to identify patterns suggestive of specific genetic and environmental causes, including developmental field defects, sequences, syndromes, and associations (Table 3). A developmental field defect is a "pattern of anomalies derived from the disturbance of a single developmental field". (16) A sequence is a "pattern of multiple anomalies derived from a single known or presumed previous anomaly or mechanical factor". (16) A syndrome is a "pattern of multiple anomalies thought to be pathogenetically related and not known to represent a single sequence" or developmental field defect. (16) An association is a "nonrandom occurrence in 2 or more individuals of multiple anomalies not known to be" a developmental field defect, a sequence, or a syndrome. (16) In some cases, a pattern may be suggestive of a specific genetic diagnosis in the same way that abdominal pain, joint pain, and purpuric lower extremity exanthema are suggestive of Henoch-Schonlein purpura. (21) For a limited set of genetic conditions, the characteristic clinical findings have informed the development of online tools, including the Marfan syndrome systemic score calculator and the *PTEN*-specific risk calculator. The former determines whether a patient meets the diagnostic criteria for Marfan syndrome. Marfan syndrome is characterized by connective tissue changes, including aortic dilation, myopia, and scoliosis. The latter estimates the likelihood that *PTEN* gene testing for Cowden syndrome will be positive. Cowden syndrome is characterized by macrocephaly, a variety of mucocutaneous findings, and cancer predisposition. Access to both is available free of charge. (22)(23) It is possible that additional online tools will be developed over time and with funding.

If the pattern of clinical findings is not immediately evocative of a specific diagnosis, then it is critical to adopt an open-minded approach to the genetic differential diagnosis. This is exemplified by the set of questions ascribed to pediatrician and geneticist Barton Childs: "Why this patient? Why this disease?

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Why now?" These questions may seem open-ended to a fault. However, this "genetic lens" is crucial for considering the genetic and environmental factors influencing a patient's clinical presentation, including timing. (24) There is a growing collection of paper-based and electronic resources available to facilitate this process. For example, the Online Mendelian Inheritance in Man® (OMIM®; Johns Hopkins University, Baltimore, MD) database is a powerful and up-to-date tool that can highlight genetic conditions to consider based on 1 or more clinical findings. Access to this resource is available free of charge. (2) The POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations) and London Dysmorphology databases can be used to generate a list of diagnoses associated with specific dysmorphisms as well. (25)(26) Access to the latter resource is available free of charge through the Face2Gene smartphone application. Face2Gene uses automated facial feature analysis, in addition to the manual entry of clinical findings, to facilitate the construction of a genetic differential diagnosis. (27) When there is a history of in utero exposure(s), resources such as the Reprotox® and TOXNET® databases can be referenced. (28)(29) Access to the latter resource is available free of charge.

It can be worthwhile to systematically think through the different types of genetic variation that are possible when constructing the genetic differential diagnosis. This thought exercise is useful for ensuring that a variety of diagnoses are considered and for determining the type(s) of genetic testing that may be indicated for a patient's genetic evaluation (Table 4). A whole chromosomal aneuploidy is an extra or missing chromosome. This becomes more likely with a history of advanced maternal age. A chromosomal rearrangement is a change in the location of a piece of a chromosome. This becomes more likely with a history of recurrent pregnancy losses. A partial chromosomal structural variant is an extra or missing piece of a chromosome. This should be considered with a history of developmental delay, autism spectrum disorder, and/or multiple congenital anomalies. A single-gene variant is a change in a gene within the nuclear genome. This becomes more likely with a history of advanced paternal age, a positive family history, a specific pattern of clinical findings, etc. An imprinting variant is an extra or missing parent-of-origin–specific methylation. This becomes more likely with a history of assisted reproductive technologies. A mitochondrial genomic variant is a change in a gene within the mitochondrial genome. This becomes more likely with a positive family history suggestive of matrilineal mitochondrial inheritance.

For example, there are many genetic conditions associated with "abnormal ears" and other anomalies. Down syndrome can be characterized by small dysplastic ears, redundant nuchal skin, a protruding tongue, a flattened facial profile, epicanthal folds, an increased sandal gap, and hypotonia. It is associated with trisomy 21 or chromosomal rearrangements. (30) 22q11.2 deletion syndrome can be characterized by dysplastic ears, congenital heart defect, cleft palate, learning difficulties, immunodeficiency, seizures, and hypocalcemia. It is associated with partial deletion of chromosome 22. (31) CHARGE syndrome can be characterized by dysplastic ears and a variety of other anomalies, as previously discussed. It is associated with changes in the *CHD7* gene (and possibly also the *SEMA3E* gene). (32)(33) Beckwith-Wiedemann syndrome can be characterized by posterior helical pits, overgrowth, omphalocele, and risk of embryonal tumors. It is associated with a variety of changes involving imprinted

TABLE 3. Examples of Anomaly Patterns

Developmental field defect
Pattern of anomalies derived from the disturbance of a single developmental field.
Example: caudal regression (ie, atypical development of the lower half of the body, including the extremities)
Sequence
Pattern of multiple anomalies derived from a single known or presumed previous anomaly or mechanical factor.
Example: Pierre-Robin sequence (ie, micrognathia, leading to glossoptosis, leading to airway obstruction, often leading to cleft palate)
Syndrome
Pattern of multiple anomalies thought to be pathogenetically related and not known to represent a single sequence or developmental field defect.
Example: CHARGE syndrome (ie, coloboma, heart defect, choanal atresia, restricted growth, genitourinary anomaly, ear anomaly)
Association
Nonrandom occurrence in ≥2 individuals of multiple anomalies not known to be a developmental field defect, a sequence, or a syndrome.
Example: VACTERL association (ie, vertebral anomaly, anal atresia, cardiac anomaly, tracheoesophageal fistula, renal anomaly, limb anomaly)

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domains on chromosome 11. (34)(35) Mitochondrial genomic variants are less likely when considering the genetic differential diagnoses for ear anomalies but more likely when considering that for nonsyndromic sensorineural hearing loss. (36)(37) Mycophenolate mofetil embryofetopathy can be associated with anotia or other ear anomalies, ocular anomalies, and orofacial clefting; it is a consequence of teratogenic exposure. (38)

Once the genetic differential diagnosis has been constructed and carefully considered, then the optimal genetic testing strategy can be planned. This often includes a chromosomal microarray, which is recommended as first-line genetic testing for the genetic evaluation of multiple congenital anomalies, autism spectrum disorder, and intellectual disability. (39) It is indicated for the evaluation of possible partial chromosomal structural variant. Beyond this, the approach to genetic testing should be focused on the most likely genetic conditions and/or types of genetic variation. Karyotype is indicated for the evaluation of possible whole chromosomal aneuploidy or chromosomal rearrangement. Single- or multi-gene testing is indicated for the evaluation of possible single-gene variant. Methylation analysis is indicated for the evaluation of possible imprinting variant. Mitochondrial gene testing is indicated for the evaluation of possible mitochondrial genomic variant. It is important to ask about and learn of previous genetic testing before ordering a genetic test. Repeating a genetic test is not expected to yield a different result, only added cost and several weeks' delay to the patient's genetic evaluation. As a result, the 5 recommendations by the American College of Medical Genetics and Genomics through the Choosing Wisely® campaign include "Do not order a duplicate genetic test for an inherited condition unless there is uncertainty about the validity of the existing test result." (40) It is worth having any previous genetic testing results available. Word-of-mouth reports can be unreliable, and unhelpful during discussions with consultants. A few of the additional intricacies of genetic testing are addressed in the article "Genetic Counseling in Pediatrics" published in the July 2018 issue of *Pediatrics in Review.* (41)

Precise word choice is critical when communicating with patients and their families regarding genetic test results and diagnoses. For example, a "positive" test result may not be considered good news by parents dreading the possibility that their child has a genetic "disorder." In contrast, a "negative" test result may be considered bad news by parents pursuing an end to their child's "diagnostic odyssey." Value-laden terms such as *disorder* can be avoided by adopting the words the family uses or more neutral options such as *condition.* Furthermore, it is important to remember that patients are not defined by their genetic conditions. Many may not even consider themselves to have a condition. For example, the National Association

TABLE 4. **Examples of Genetic Variation Types**

Whole chromosomal aneuploidy
An extra or missing chromosome
Genetic testing: karyotype analysis
Chromosomal rearrangement
A change in the location of a piece of a chromosome
Genetic testing: karyotype analysis
Partial chromosomal structural variant
An extra or missing piece of a chromosome
Genetic testing: chromosomal microarray analysis
Single-gene variant
A change in a gene within the nuclear genome (eg, nucleotide sequence change, extra piece, missing piece), repeat expansion
Genetic testing: single-gene sequencing and/or deletion/duplication analysis, multi-gene panel sequencing and/or deletion/duplication analysis, clinical exome sequencing, repeat expansion analysis
Imprinting variant
Extra or missing methyl group modification
Genetic testing: DNA methylation analysis
Mitochondrial genomic variant
A change in a gene within the mitochondrial genome (eg, nucleotide sequence change, missing piece)
Genetic testing: mitochondrial genome sequencing and/or deletion analysis

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of the Deaf prefers to define the term *deaf* as the "audiological condition of not hearing" and the term *Deaf* as the "particular group of deaf people who share a language—American Sign Language (ASL)—and a culture." (42) Similarly, the Little People of America has advocated for the use of their given names or preferred terms such as *little people* and *dwarfs*. (43) Communication of genetic information benefits from a thoughtful approach such as the SPIKES protocol for disclosing information in the oncology setting. The acronym SPIKES represents the 6 steps of the protocol: 1) Setting up the interview, 2) Assessing the patient's perception, 3) Obtaining the patient's invitation, 4) Giving knowledge and information, 5) Addressing the patient's emotions with empathetic responses, and 6) Strategy and summary. (44)

PATIENT 1 REVISITED

The family history is notable for multiple paternal relatives with macrocephaly. You acknowledge that larger heads can run in families and not amount to anything beyond difficulties finding hats that fit. However, you identify additional concerns. His paternal aunt was diagnosed as having breast cancer at 37 years old. His paternal grandfather was diagnosed as having nonmedullary thyroid cancer recently. This seems like too many things affecting more than 2 relatives. There is a clear autosomal dominant inheritance pattern. Additional careful questioning reveals that his father also has penile freckling. You measure the child's head circumference, which is beyond the 95th percentile for age and sex. A quick query of OMIM for these features suggests the diagnosis of Cowden syndrome. You also find the online *PTEN*-specific risk calculator, which suggests a high probability of finding a pathogenic variant. (23) You refer your patient and his family for genetic counseling and *PTEN* gene testing. After a few weeks, the diagnosis of Cowden syndrome is molecularly confirmed for him, his father, and several paternal relatives. At first, the entire family finds it hard to handle this life-changing information. However, it also means that his 35-year-old father undergoes screening colonoscopy in time to have a precancerous lesion removed. (45)

PATIENT 2 REVISITED

The family history seems unremarkable. However, you remind yourself that traits can be genetic but not inherited. Her hypertelorism, hypermobility, and bifid uvula seem specific, and potentially significant. For example, although isolated bifid uvula can be observed in the general population, your literature review reminds you that it may be a marker of submucous cleft palate. A submucous cleft palate can be difficult to detect and has surgical implications. (46)(47) A quick query of OMIM for these features suggests several possible diagnoses, including spondylodysplastic Ehlers-Danlos syndrome, Shprintzen-Goldberg syndrome, and 3 different types of Loeys-Dietz syndrome. As you review the OMIM clinical synopsis for each genetic condition, it seems difficult to determine which is the most likely because many of the clinical findings are nonspecific. However, you identify several "can't miss" cardiovascular anomalies. You refer your patient for genetic evaluation and order an echocardiogram, which reveals a bicuspid aortic valve. By the time she is seen by the geneticist and genetic counselor she has more noticeable arachnodactyly and velvety skin. The family elects to proceed with *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2* gene panel testing for Loeys-Dietz syndrome. After a few weeks, her parents are notified that she has a de novo pathogenic variant in the *TGFBR2* gene. A repeated echocardiogram reveals aortic root dilation. She begins treatment with an angiotensin receptor blocker under the guidance of an expert in genetic aortopathies. She tolerates this well as her aortic root diameter *Z* score stabilizes, then normalizes. (48)

CONCLUSION

A genetic diagnosis can have life-changing implications for our patients and their families. However, the diagnostic odyssey undertaken to reach this point is often protracted. It can take a few years for patients to receive a diagnosis, even for those with well-described genetic conditions such as 22q11.2 deletion syndrome. (49) This process may involve multiple subspecialists and misdiagnoses when the clinical picture is complex and/or characterized by nonspecific findings, as is often the case with primary mitochondrial conditions. (50) It is important to remember that the natural variation in physical features, further influenced by familial resemblances and ethnicity, can obscure the classical craniofacial features described for genetic conditions such as 22q11.2 deletion syndrome. (49) As is the case with other pediatric presentations, syndromic patterns of distinctive findings require systematic responses. Even when the possibility of a genetic condition is recognized and a referral is placed, patients and their families often need to wait for several months for an appointment with a geneticist. This process is sometimes driven by mothers and fathers seeking answers, often without medical expertise, but always with expertise in their children. With time, they often develop a familiarity with rare and ultra-rare conditions that can surpass that of most health-care professionals and scientists. (51) In these cases, the pediatrician can partner with these families, listen to their concerns, and work toward timely evaluation. This may include basic laboratory and imaging studies.

Several approaches are poised to address the need for genetics services. For example, telemedicine has been used to improve access and has been well-received. (52) There is increasing patient interest in the use of social media, at least for the

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purposes of increasing awareness and education. (53) It is possible that general pediatrician-driven genetic evaluations will be facilitated and/or necessitated by continued development of the newborn screening program and its associated resources. (6) For example, a recent multistate study explored the possibility of newborn screening for fragile X syndrome. (54) Eventually, general pediatrician involvement in other standardized genetic evaluations and treatment may become common practice.

Currently available online resources such as the OMIM database have revolutionized the genetic diagnostic process. (2) Automation and standardization of other difficult and time-consuming processes are likely to play a role in the future, including facial feature analysis with smartphone applications and basic genetic counseling with chatbots. (27)(55) It is possible to use natural language processing for the automated extraction of family history data from the electronic medical record. (56) It is also possible to automate the identification of high-risk pedigrees collected using online family history tools, as well as subsequent referrals. (57) Eventually, it may be possible to interrogate the electronic medical record data and use Bayesian frameworks to automatically generate probability-ranked differential diagnoses. (58) Quantitative mathematical approaches such as this are potentially applicable to the analysis of expansive genomic data for variant pathogenicity assessments as well. (59) It is even possible that all newborns will be screened for genetic conditions using exome sequencing or another paradigm-shifting test method not yet dreamed up. (60)

As genetic medicine continues to rapidly evolve, we must remember, as articulated by Judith G. Hall: “Each family seen in the clinic has been through emotional trauma, is facing difficult decisions, and will end up with less than ideal solutions. Remaining sensitive and open is challenging and requires training and practice. Providing the relevant information clearly and ensuring that each family member feels supported are special skills. Dealing with such significant problems might seem depressing, but providing families with new perspectives, multiple options, and reliable information for their life journey is enormously rewarding.” (51)

Summary

- Based on level D evidence (expert opinion, case reports, reasoning from first principles), dysmorphology is an art and science of precise clinical reasoning that addresses the variation of physical features. (7)(16)
- Based on level D evidence (expert opinion, case reports, reasoning from first principles), the family history is an important source of genetic information. Recognizable inheritance patterns include autosomal dominant, autosomal recessive, X-linked, and mitochondrial genomic. (11)
- Based on level D evidence (expert opinion, case reports, reasoning from first principles), it is useful to consider the different types of genetic and nongenetic changes that are associated with physical changes when constructing genetic differential diagnoses, which ultimately determines the optimal genetic testing strategy.
- Based on level D evidence (expert opinion, case reports, reasoning from first principles), resources available to pediatricians include the Elements of Morphology, the *Handbook of Physical Measurements, Smith’s Recognizable Patterns of Human Malformation,* the Online Mendelian Inheritance in Man® database, and the London Dysmorphology database (available through the Face2Gene smartphone application). (2)(8)(17)(18) (27)
- Based on level D evidence (expert opinion, case reports, reasoning from first principles), it is important to ask about and learn of any previous genetic testing before ordering a genetic test.
- Based on level D evidence (expert opinion, case reports, reasoning from first principles), it is important to be precise and careful in word choice when discussing genetic testing results and genetic diagnoses.

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/40/12/609.supplemental.**

Dysmorphology

Alexander Y. Kim, MD*
Joann N. Bodurtha, MD, MPH*†

*McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
†Departments of Pediatrics and Oncology, Johns Hopkins University School of Medicine, Baltimore, MD

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1. You are seeing a 7-year-old girl in your office who is new to your practice. She comes with her mother and father. The child has multiple café-au-lait macules and axillary and inguinal freckles. She has normal growth parameters. She is receiving an Individualized Education Plan for reading. Her parents do not have any café-au-lait macules or axillary/inguinal freckles. Which of the following is the most accurate statement regarding the potential diagnosis given this child's clinical findings?
   - A. Genetic testing for neurofibromatosis type 1 (NF1) will provide a definitive answer as to whether this child has NF1.
   - B. Given the absence of neurofibromas at this age, a diagnosis of NF1 is unlikely.
   - C. NF1 is unlikely because this is an autosomal dominant condition and she would have had to inherit her *NF1* gene from her mother or father.
   - D. The absence of a negative family history of NF1 does not rule out the possibility of a diagnosis of NF1.
   - E. The risk of this child's future offspring having NF1 is negligible given the uncertainty of a clinical diagnosis.
2. You are called to the delivery room to attend the delivery of a baby boy born to a 25-year-old gravida 1 para 0 woman. Her pregnancy was complicated by oligohydramnios and renal agenesis. The baby is born vaginally with Apgar scores of 7, 5, and 3 at 1, 5, and 10 minutes, respectively. The baby is intubated and transferred to the NICU. On physical examination he was noted to have midface flattening, multiple joint contractures, and hip dysplasia. Which of the following statements best describes the pathophysiologic cause(s) of the clinical features in this patient?
   - A. Amnion disruption.
   - B. Early urethral obstruction sequence.
   - C. Multiple deformations only.
   - D. Single malformation only.
   - E. Single malformation with various physical features due to deformations, secondary to the underlying malformation.
3. You are the attending covering the well-baby nursery. An African American baby boy is admitted to the nursery. He is born with postaxial polydactyly of the hands and feet. The baby's mother had no prenatal care. She denies the use of alcohol and other illicit substances or medications during pregnancy. Both parents are available. Which of the following is the most appropriate next step in this patient?
   - A. Chromosome microarray study.
   - B. Clinical genetics consult.
   - C. Complete physical examination and family history for similar problems.
   - D. Genetic testing for the *GLI3* gene.
   - E. Skeletal survey.
4. A newborn female infant is transferred to the NICU shortly after birth due to polyhydramnios. On physical examination she is noted to have small dysplastic ears, redundant nuchal skin, a protruding tongue, a flattened facial profile, epicanthal folds, an increased sandal gap, and hypotonia. Family history is significant for recurrent miscarriages in the mother. Which of the following is the most appropriate genetic test to order that will most likely confirm the diagnosis in this patient?
   - A. Aortopathy gene panel.
   - B. DNA methylation for Prader-Willi/Angelman syndrome.
   - C. Fluorescence in situ hybridization (FISH).
   - D. Karyotype analysis.
   - E. Subtelomeric FISH analysis.

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5. You live in a remote town and are following up with a family in which the mother has Waardenburg syndrome (a genetic condition associated with heterochromia of the eyes, hearing loss, and abnormal spacing of eyes). The mother's male child is tested for the familial genetic mutation in Waardenburg syndrome because he failed the newborn hearing screen. Genetic testing indicates that the child has a *PAX3* mutation. The geneticist calls you with the results and asks you to relay the information to the baby's family. You plan to contact the family and meet with them in person at their next clinic visit. Which of the following statements is the most appropriate way to communicate the test results to the family during your initial meeting with them?
    - A. "Because your child was identified after birth with hearing loss, we suspect that he will have a more severe clinical course than his mother."
    - B. "The genetic test performed indicated that your baby has the same genetic change as his mother and he is likely to have clinical features associated with Waardenburg syndrome."
    - C. "The genetic test results were positive and indicate your baby has the same disease as his mother."
    - D. "The genetic test results were positive for Waardenburg syndrome."
    - E. "Your baby's test results for Waardenburg syndrome were positive. Your diagnostic journey is now complete."

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Dysmorphology

Alexander Youngjoon Kim and Joann Norma Bodurtha

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Congenital Anomalies of the Kidneys, Collecting System, Bladder, and Urethra

Halima S. Janjua, MD,* Suet Kam Lam, MD, MPH, MS,† Vedant Gupta, DO,‡ Sangeeta Krishna, MD†

*Center for Pediatric Nephrology, †Department of Pediatric Hospital Medicine, ‡Department of Pediatrics, Cleveland Clinic Children's, Cleveland, OH

Education Gap

Several congenital anomalies of the kidney and urinary tract are incidental findings. An understanding of when to suspect and how to diagnose, manage, and use timely and appropriate investigations and consults is necessary.

Objectives

After completing this article, readers should be able to:

1. Develop an awareness of various congenital anomalies of the renal system, including embryology, prevalence, and risk factors.
2. Describe the clinical presentation and management of renal and urinary tract anomalies, including which anomalies warrant further evaluation and the timing and utility of imaging modalities.
3. Develop an awareness of genetic syndromes affecting the kidneys and urinary tract with associated extrarenal manifestations.

INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) include a wide spectrum of anomalies, with a reported incidence of up to 2% of births. (1) CAKUT account for almost one-fourth of all birth defects. (2) These are major causes of kidney disease in children and account for more than 40% of end-stage renal disease (ESRD). CAKUT are usually detected by routine prenatal ultrasonography, although some cases are not diagnosed until adulthood. (3)

When renal disease is suspected, a complete physical examination should be performed with particular focus on accurate blood pressure measurement; the abdomen for palpable kidneys and a distended bladder; the genitalia for the position of the meatus, penile abnormalities, and urine flow; and the back for signs of neural tube defects.

Genetics play a major role in the etiology of CAKUT as family history is identified in 10% to 50% of affected children (Table). (4)(5) Similarly, 23% of asymptomatic first-degree relatives are found to be affected on screening. (4) Many environmental factors, such as maternal medication exposure, folate and iron deficiency, and diabetes mellitus, also contribute to the expression of CAKUT.

PATHOGENESIS

Human kidneys develop in 3 stages: the pronephros, the mesonephros, and the metanephros. The pronephros and the mesonephros involute, and the metanephros

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ABBREVIATIONS

ARPKD	autosomal recessive polycystic kidney disease
CAKUT	congenital anomalies of the kidney and urinary tract
ESRD	end-stage renal disease
MCDK	multicystic dysplastic kidney
PUV	posterior urethral valve
RBUS	renal and bladder ultrasonography
UPJ	ureteropelvic junction
UTI	urinary tract infection
UVJ	ureterovesical junction
VCUG	voiding cystourethrogram
VUR	vesicoureteral reflux

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forms the kidney starting at the fifth week of embryogenesis. The kidneys lie in the pelvis initially, where they are adjacent to each other and facing ventrally. By the eighth week of embryogenesis, the kidneys migrate to their permanent location in the lumbar region, and by the tenth week, they start producing urine. At the time of birth, each healthy kidney measures approximately 4.0 to 4.5 cm in the longest dimension. With the co-expression of multiple signaling and transcription factors, there are reciprocal interactions between the metanephros and ureteric epithelium, resulting in the formation of nephrons and the collecting system. In the meantime, the bladder develops from the urogenital sinus. Malfunctioning of otherwise well-controlled signaling pathways and transcription factors can result in CAKUT. (6)

ANOMALIES OF THE KIDNEY

Renal Agenesis

Renal agenesis or aplasia is a missing kidney, with the former a result of embryologic lack of initiation of development and the latter of failure to progress after initial induction and subsequent involution. The incidence of unilateral renal agenesis is 1 in 1,000 to 1 in 3,000 live births, with males and the left side disproportionately affected. (7)(8) Diagnosis is usually made on routine prenatal ultrasonography without obvious physical examination signs or symptoms, although there is a 50% rate of coexisting urogenital abnormalities. During fetal development, the contralateral kidney undergoes hypertrophy as a compensatory response to the effects of a decreased nephron count. The single hypertrophied kidney hyperfiltrates and develops renal injury marked by hypertension, proteinuria, and reduced glomerular filtration rate. (9) Hence, serial ultrasonography and routine screening for hypertension and proteinuria into adulthood are warranted. In a study, the median age at renal injury was 14.8 years in a cohort of 151 pediatric patients with a solitary functioning kidney. (10) Bilateral agenesis has a male predominance and is rare, occurring in 1 in 7,000 to 1 in 10,000 births. (11) Those affected generally do not survive after birth because oligohydramnios leads to the Potter sequence, with multiple anomalies of the lung, limb, and face.

Renal Dysplasia

A dysplastic kidney occurs due to abnormal differentiation after initiation of normal development and is one of the most common causes of pediatric ESRD. Prevalence ranges from 0.1% on ultrasonography screening to 4% in infant autopsies. (12) Unilateral dysplasia is more common than bilateral dysplasia, and as many as 50% to 75% of cases are associated with urinary tract anomalies, such as horseshoe kidney, ureteral duplication, hydroureter, ureteropelvic junction (UPJ) and ureterovesical junction (UVJ) obstruction, and vesicoureteral reflux (VUR). (13) Although renal and bladder ultrasonography (RBUS) can capture a small hyperechoic kidney, histologic analysis can show undifferentiated tissue, nephron cell structure, and the presence of cartilage and cysts. Unilateral dysplasia has a good prognosis, barring the severity of comorbidities of concomitant anomalies. However, unilateral renal dysplasia also may lead to death due to the Potter sequence or chronic kidney disease.

Multicystic Dysplastic Kidney

The most common cause of a congenital solitary kidney is unilateral multicystic dysplastic kidney (MCDK). The prevalence of MCDK is 1 in 2,400 to 1 in 4,300 live births, and it disproportionately affects males and the left side. (14) Most MCDKs involute without intervention (60% by age 10 years) and have minimal functional nephrons or renal tissue. (15) Most cases of MCDK are detected prenatally via ultrasonography, and they are the second most common cause of newborn abdominal masses, with hydronephrosis being the first. There are many isolated cysts of differing sizes with dysplastic stroma associated with an atretic ureter on gross examination. The contralateral kidney may be affected by low-grade VUR in 15% to 28% of patients or by UPJ obstruction in 4% of patients. (15)(16) Serial postnatal RBUS is warranted to monitor for contralateral renal abnormalities, growth, and involution. If involution occurs, further RBUS is not necessary. Malignant transformation (Wilms tumor or renal cell carcinoma) is rare; therefore, nephrectomy of MCDK is no longer the treatment of choice. (14) Conservative management with regular screening for hypertension and proteinuria is needed in patients with MCDK.

Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease (ARPKD) is an inheritable genetic disorder with an incidence of 1 in 10,000 to 1 in 40,000 live births. (17) Although ARPKD can present later in life, it is typically thought of as an "infantile" disease. Prenatal ultrasonography shows bilateral enlarged hyperechoic kidneys and possibly oligohydramnios. Although 30% of newborns with ARPKD die after birth, postinfancy survival is 80% at 10 years. (17) Most infants develop difficult to control hypertension, and 20% to 45% have ESRD by age 15 years. (18) On examination at birth, patients have bilateral firm abdominal masses and possibly respiratory distress. Laboratory work will show increasing blood urea nitrogen and serum creatinine levels, indicative of renal insufficiency. The bilateral renal cystic disease and associated hepatic fibrosis lead to renal and hepatic

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insufficiency. Although renal impairment can be variable, all patients have hepatic fibrosis.

Diagnosis is made by imaging and the infant having at least 1 of the following: both parents without renal cysts, a sibling with ARPKD, consanguineous parents, or hepatic fibrosis. Management of the infant may include respiratory support, hypertension control, or fluid and electrolyte support. Nephrectomy may be an option if the enlargement is severe enough to affect respiratory or digestive function. As the patient grows older, dialysis for advanced kidney disease or surgery for portal hypertension may be required.

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease is the most common inheritable genetic renal cystic disease, with an incidence of 1 to 2 in 1,000 live births. (17) Genetic testing is usually reserved for unclear diagnosis or if a family member is being considered for kidney donation for transplant.

Although this disease generally presents later in life (30–40 years of age), it can present in infancy with a poor prognosis. Clinical presentations may range from abdominal masses in the newborn to abdominal or flank pain between the third and fifth decades of life. Hematuria, hypertension, or gastrointestinal symptoms may be seen in adults. Hypertension occurs in half of the patients by their third decade of life and in almost all patients with ESRD. Other complications include hematuria, urinary tract infection (UTI), cerebral aneurysm, or heart disease, with mitral valve prolapse as the most common valvular disorder. (17) Extrarenal manifestations occur most commonly in the liver, followed by cysts in the seminal vesicles, arachnoid membrane, and pancreas. (19) In contrast to ARPKD, macroscopic cysts are seen on ultrasonography. Asymptomatic children with affected parents should be screened annually with blood pressure measurements and urinalysis. Management includes supportive care for respiratory or renal issues in infancy and long-term medical management of renal insufficiency and hypertension. Patients presenting with flank or abdominal pain and/or fever should be evaluated for infection, urinary stones, or tumors. Nephrectomy may be performed in selective symptomatic patients.

ANOMALIES OF THE COLLECTING SYSTEM

Hydronephrosis

Hydronephrosis is the dilation of the renal pelvis and calyces secondary to increased urine retention. In 50% to 75% of the cases, hydronephrosis is transient or physiologic. Other causes, such as UPJ obstruction and VUR, have an incidence of 10% to 30%. Less common causes include UVJ obstruction, MCDK, or posterior urethral valves (PUVs). (20) A complete physical examination should be performed with particular focus on the lower abdomen for a distended bladder, genitalia for penile abnormalities and urine flow, and the back for signs of neural tube defects, which may be associated with a neurogenic bladder. (21) Blood work assessing kidney function is generally withheld, except in bilateral hydronephrosis and severe cases.

RBUS is useful in determining the severity of hydronephrosis, for which multiple classification systems exist. The urinary tract dilation classification system is widely used, which includes parameters on anteroposterior renal pelvic diameter, calyceal dilation, parenchymal thickness and appearance, and ureter and bladder abnormality. (20) The Society for Fetal Urology classifies diseases on the anteroposterior renal pelvic diameter and on the appearance of the kidney, ureter, and bladder. (22) Postnatally in a low-risk patient with unilateral hydronephrosis, RBUS can be performed 7 to 10 days after birth. (20)(23) Exceptions to delayed imaging include cases of oligohydramnios, urethral obstruction, bilateral high-grade dilation, and follow-up concerns. (23) In bilateral hydronephrosis or a high-risk infant with bladder dilation, delivery at a center with pediatric urology support is recommended. A high-risk maternal/fetal medicine specialist should be involved when there are findings of oligohydramnios. If the lower urinary tract is involved and there is bladder distention and/or bilateral hydroureteronephrosis, voiding cystourethrography (VCUG) should be performed to rule out PUVs, and initiation of antibiotic prophylaxis is recommended. (20)

Vesicoureteral Reflux

VUR is the most common pediatric urologic condition, affecting up to 30% of children with a febrile UTI and 0.4% to 1.8% of the general pediatric population. (24) In infants with prenatal hydronephrosis, 10% to 20% will have VUR. It is seen in 50% of children of parents with VUR and 25% of siblings with VUR. (25) Primary reflux is an embryonic anatomical defect and largely spontaneously self-resolves with elongation of the intravesical tunnel at the UVJ as the child grows. Secondary VUR occurs when increased intravesical pressures lead to retrograde urine flow past the normal UVJ. This can be due to disorders such as neurogenic bladder, PUVs, or bowel and bladder dysfunction in anatomically normal children. Correction of bowel and bladder dysfunction may resolve VUR. (26)

Management of VUR is controversial and may include antibiotic prophylaxis and/or surgical correction, taking into consideration patient age, severity, renal scarring, and parental preference. A meta-analysis that included the RIVUR (Randomized Intervention for Children with Vesicoureteral Reflux) and PRIVENT (Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts) studies demonstrated that although antibiotic

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prophylaxis can reduce UTIs, it does not reduce kidney scarring. (27) Furthermore, antibiotic-resistant bacteria increasingly cause infections while the patient is on prophylaxis. Complications of VUR include pyelonephritis, renal scarring, hypertension, and chronic kidney disease.

Duplicated Collecting System

Duplications of the collecting system are the result of abnormal embryonic origins. Complete duplication is a double ureter, each draining separately into the bladder, whereas partial duplication presents with a bifid ureter with a single drain into the bladder. (28) VUR is usually present in the lower moiety of a duplicated collecting system, whereas the upper moiety is associated with an obstructive ectopic ureter, with or without a ureterocele. The prevalence of ureteral duplications is less than 1% of the general population and affects females 2 to 4 times more often than males. (29) Complications of a duplicated collecting system include VUR, obstruction, ectopic ureteral insertion, and ureteroceles. (28) Ultrasonography is the mainstay of diagnosis, both before and after birth, and is the most common modality for incidental findings of duplication. (30) VCUG can help determine VUR and voiding patterns. Management differs widely, based on anatomical abnormality, function, and VUR severity.

ANOMALIES OF THE BLADDER

Congenital Neurogenic Bladder

Bladder dysfunction results from disruptions of the normal voiding process by neurogenic, anatomical, or functional causes. (31) The most frequent neurogenic cause is spinal dysraphism, a spectrum of congenital abnormalities that includes open and closed forms. Folic acid deficiency is the major etiology for these disorders and leads to the failure of complete closure of the spinal neural tube. (32) Other less common risk factors include chromosomal abnormalities and gene mutations. (33) The estimated incidence of spinal dysraphism is approximately 0.1%. (34) However, the incidence has been declining worldwide during the past few decades due to better nutrition and supplementation for pregnant mothers and improved prenatal care. (35) Other neurogenic etiologies include sacral agenesis, cerebral palsy, and traumatic spinal cord injuries.

Myelomeningocele is the most common and severe form of neural tube defects and accounts for 85% of all open spinal dysraphisms. (36) A myelomeningocele involves an opening in the spine where both nerve roots and spinal cord tissue protrude into a fluid-filled sac on the back. (34) Due to incomplete closure of the vertebral column and the risk of exposed spinal canal contents, urgent evaluation and treatment are needed. As many as 60% of all cases have some form of bladder dysfunction and nearly all cases of myelomeningocele are associated with a neurogenic bladder. (36)(37) The initial evaluation should include a neurologic examination. Checking muscle mass, tone, spontaneous movements, deep tendon reflexes, and skinfolds can help determine neurologic function and localize the dysraphism level. Of note, the level of dysraphism is poorly predictive of bladder dysfunction, and a separate complete bladder evaluation is recommended. (38)

Secondary VUR occurs when increased intravesical pressures lead to retrograde urine flow past the normal UVJ. This can be due to disorders such as a neurogenic bladder, PUVs, or bowel and bladder dysfunction in anatomically normal children. Correction of bowel and bladder dysfunction may resolve VUR. (31)(38) Early determination of bladder function allows for more proactive treatment and will guide future surveillance and management. (31)(38)(39)

No intervention is necessary if complete bladder emptying is noted, regardless of the degree of bladder denervation. Any sign of bladder dyssynergy, incontinence, incomplete emptying, or urinary tract abnormalities warrants further intervention. Treatment is guided by the initial assessment and may include anticholinergic medications and intermittent or continuous catheterization. If symptoms worsen despite initial treatment, then surgical intervention is indicated. (39)(40)(41)(42) Failure to intervene early can lead to high-grade VUR and recurrent UTIs, leading to irreversible renal injury. Patients with congenital neurogenic bladder will need regular surveillance visits and imaging to monitor the urinary tract and bladder function. (38)(41) Patients born with spinal dysraphism can have secondary spinal cord injury over time associated with growth and fibrosis. (43) Prognosis for these patients has dramatically improved in the past 3 decades due to advancements in detection, minimally invasive therapies, and higher levels of urologic care. (38)

ANOMALIES OF THE URETHRA

Posterior Urethral Valves

PUVs are characterized by abnormal mucosal folds at the prostatic urethra level that function as a valve to obstruct urine flow. (44) They are the most common cause of congenital urethral obstruction, affecting 1 in 5,000 to 1 in 25,000 live male births. (45)(46) Prenatal ultrasonography may show bilateral hydronephrosis, a thick-walled bladder, dilated posterior urethra, and/or oligohydramnios. (45) If not diagnosed prenatally, PUVs can present in newborns with intrauterine growth retardation and a weak voiding stream. Older children can present with recurrent UTIs, urosepsis, renal failure, or incontinence. VCUG remains the gold standard for detecting PUV and will show the proximal urethra more

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dilated than the urethra distal to the valve. A urethral catheter should be placed in the bladder to relieve the obstruction. (46) The treatment of choice is transurethral valve ablation, with diversion of the obstructed bladder via vesicostomy as an alternative. (47) PUVs continue to have high mortality and morbidity (48) and are the most common cause of obstructive uropathy leading to ESRD. (49)(50)

Eagle-Barrett syndrome, also known as prune belly syndrome, is a rare lower urinary tract malformation affecting 1 in 30,000 newborns, with 95% of patients being males. (51) Prenatal ultrasonography reveals findings similar to PUVs. Diagnosis at birth is established clinically with pathognomonic findings of deficiency of abdominal wall musculature with loose and wrinkled overlying skin and bilateral cryptorchidism. RBUS reveals dilation of the urinary tract secondary to urethral obstruction. (52) Nearly 50% of patients have associated cardiovascular, gastrointestinal, or orthopedic malformations, and all patients have some degree of renal dysplasia. (53) These patients have a high incidence of chronic kidney disease, with 40% to 50% of patients needing renal replacement therapy. (54)

Urethral Stricture

Congenital urethral strictures are a rare urethral anomaly. These patients can be identified prenatally with abdominal imaging findings similar to PUV. (55) After birth, patients present with obstructive and irritative symptoms, such as

TABLE. Genetic Syndromes Associated with CAKUT

SYNDROME	RENAL ABNORMALITY	EXTRARENAL MANIFESTATIONS
Turner	Renal agenesis, hypoplasia	Short stature, amenorrhea, webbed neck, cubitus valgus, hypogonadism
Down	Renal agenesis	Intellectual disability, hypotonia, congenital heart disease, clinodactyly
Patau	Renal agenesis	Holoprosencephaly, midline anomalies, cleft lip/palate
CHARGE	Many urinary tract malformations	Cardiac defects, cleft palate, hearing loss, coloboma, choanal atresia, genital anomalies
Di George	Renal agenesis, dysplasia, VUR	Cardiac defects, cleft palate, thymic aplasia, hypocalcemia, immunodeficiency
Renal coloboma	Renal hypoplasia, MCDK, VUR	Optic disc/nerve anomalies, hearing loss, CNS and genital anomalies, skin and ligamentous laxity
Orofaciodigital	Renal cysts	Lobed tongue, cleft palate, hypodontia, micrognathia clinodactyly
Branchio-oto-renal	Renal agenesis, dysplasia	Lateral cervical fistulas or cysts, ear pits, hearing loss
Renal cysts and diabetes	Renal dysplasia, cysts	Diabetes mellitus
Fraser	Renal agenesis, dysplasia	Cryptophthalmos, syndactyly, tracheal stenosis/atresia, ambiguous genitalia, craniofacial anomalies
Alagille	MCDK, renal dysplasia, mesangiolipidosis	Chronic cholestasis, cirrhosis, cardiac anomalies, butterfly vertebrae, dysmorphic facies
Bardet-Biedl	Renal dysplasia, calyceal malformations	Obesity, intellectual disability, retinal dystrophy, polydactyly
Beckwith-Wiedemann	Nephromegaly, nephrocalcinosis, medullary sponge kidney	Macrosomia, hemihyperplasia, macroglossia, omphalocele
Simpson-Golabi-Behmel	Variety of kidney and urinary tract malformations	Craniofacial anomalies, organomegaly, tumors, intellectual deficiency
Smith-Lemli-Opitz	Renal hypoplasia	Syndactyly, microcephaly, intellectual disability, heart, lung, and gastrointestinal abnormalities
Rubinstein-Taybi	Variety of kidney malformations	Highly arched eyebrows, high-arched palate, micrognathia, internally deviated toes and thumbs, hirsutism, heart and eye abnormalities

Abbreviations: CAKUT=congenital anomalies of the kidney and urinary tract, CNS=central nervous system, MCDK=multicystic dysplastic kidney, VUR=vesicoureteral reflux.

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urinary retention, dysuria, or weak stream. Diagnosis is made with VCUG, and treatment is with urethral dilatation, endoscopic repair, or vesicostomy if severe. Acquired urethral strictures are usually due to urethral instrumentation but can have inflammatory and traumatic etiologies as well. (56)

Hypospadias

Hypospadias is the most common malformation of the male genitalia, with an incidence of 0.3% to 0.5% in live male births. (57) It results in abnormal ventral placement of the urethral opening anywhere along the penis, scrotum, or perineum. Hypospadias is a clinical diagnosis and is usually made during the newborn examination. Hypospadias can present in older children and teens with a weak, downward-angled stream and, when associated with chordee, painful sexual intercourse. (58) The examination should focus on identifying other associated anomalies, the exact anatomical location of the meatus, assessment of the foreskin, and the presence of chordee. Newborn circumcision is contraindicated because the foreskin may be used for urethral and penile reconstruction. Surgical repair is elective and is ideally performed at 6 to 12 months of age. (59)

Epispadias

Epispadias is a congenital malformation of the urethra that can present as an isolated finding or can be associated with bladder exstrophy, a condition referred to as the exstrophy-epispadias complex. Epispadias is found in nearly all cases of bladder exstrophy and has an incidence of 1 in 30,000 live births, with a male preponderance. (60) Epispadias presents as a partial or complete opening of the urethral meatus on the dorsal surface. In males, the urethral meatus can be located anywhere from the distal penile shaft to the pubic area. (61) In females, epispadias is associated with a bifid clitoris and anteriorly displaced vaginal orifice. (62) Isolated epispadias is much less common, with an incidence of 0.5 in 100,000 live births in males and an even lower incidence in females. (61) Epispadias is usually evident on examination at birth and is strongly associated with urinary incontinence. RBUS should be performed to assess the urinary tract. (62) Surgical repair should be pursued as early as possible for both sexes. To maintain bladder function and continence, these patients may need multiple surgeries throughout their lifetime. (62)

GENETIC SYNDROMES ASSOCIATED WITH CAKUT

There is increasing evidence of genetic abnormalities as the cause of CAKUT. Identifying the underlying genetic involvement may improve identification and management of extrarenal manifestations. There are more than 500 genetic syndromes with renal or urinary tract abnormalities. (5)

Summary

- Based on strong research evidence, hydronephrosis is the most common cause of abnormal prenatal ultrasonography and abdominal masses in newborns. The urinary tract dilation classification system and the Society for Fetal Urology classification system are widely used for disease severity classification and management. (20)(22)
- Based on strong research evidence, vesicoureteral reflux is the most common pediatric urologic condition, affecting up to 30% of children with a febrile urinary tract infection and 0.4% to 1.8% of the general pediatric population. (24) Management remains a controversial topic and is the subject of ongoing research.
- Based on consensus, ultrasonography is the imaging of choice for initial evaluation prenatally and after birth to evaluate congenital anomalies of the kidney and urinary tract and is the image of choice for the initial evaluation of various diagnoses, to classify severity of disease, and to guide future monitoring.
- Based on strong research evidence, posterior urethral valves are most commonly diagnosed prenatally with ultrasonography findings of bilateral hydronephrosis, dilated posterior urethra, and/or oligohydramnios. (45) Based on some research evidence as well as consensus, the treatment of choice is transurethral valve ablation. (47)
- Based on strong research evidence, hypospadias is the most common malformation of the male genitalia. Newborn circumcision is contraindicated in these patients, and surgical repair is ideally performed at 6 to 12 months of age. (60)

SUGGESTED QUALITY IMPROVEMENT PROJECT

- Improve the tracking of the multidisciplinary follow-up of the patient with urinary abnormalities.

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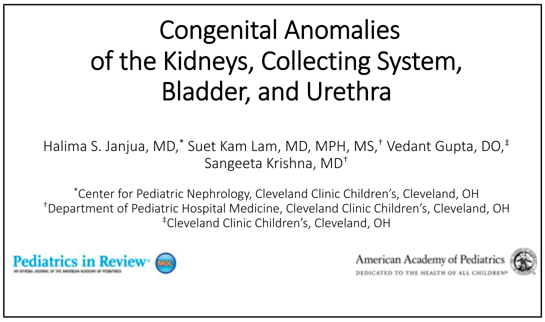

Congenital Anomalies
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Halima S. Janjua, MD,[*] Suet Kam Lam, MD, MPH, MS,[†] Vedant Gupta, DO,[‡]
Sangeeta Krishna, MD[†]

[*]Center for Pediatric Nephrology, Cleveland Clinic Children's, Cleveland, OH
[†]Department of Pediatric Hospital Medicine, Cleveland Clinic Children's, Cleveland, OH
[‡]Cleveland Clinic Children's, Cleveland, OH

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1. You are seeing a 2-week-old female newborn for her first physical examination after discharge from the nursery. She was diagnosed prenatally with a solitary left kidney by prenatal ultrasonography. You decide to order repeated renal ultrasonography today. In explaining your reasoning to the parents, which of the following statements best describes your rationale for ordering the ultrasonography today?
   - A. Only 10% of affected children have a problem in the solitary kidney, and this is just a precaution to make everyone feel better.
   - B. Renal agenesis is associated with liver cysts 30% of the time, so you need the ultrasonography to look at the liver also.
   - C. The solitary kidney is often affected by nephrocalcinosis and ultrasonography is needed to assess the extent of calcium deposits.
   - D. The solitary kidney is typically smaller than normal because of a lack of growth factors from the other kidney, and follow-up ultrasonography is needed to check its growth rate.
   - E. Up to 50% of children with 1 kidney can have a problem in the contralateral urogenital tract.

2. You are called to the newborn nursery because the nursing staff noted abdominal fullness on the right side of the abdomen while bathing a full-term male newborn infant. The baby is urinating normally, and there is no gross hematuria. On physical examination the baby is afebrile. His pulse is 120 beats/min, blood pressure is 100/60 mm Hg, and respiratory rate is 50 breaths/min. On physical examination you are able to palpate a large mass on the right side of the abdomen, and it does not cross the midline. The lungs are clear, but breath sounds are decreased on the right side. Which of the following is the most likely diagnosis in this patient?
   - A. Hydronephrosis.
   - B. Multicystic dysplastic kidney.
   - C. Neuroblastoma.
   - D. Renal cell carcinoma.
   - E. Wilms tumor.

3. You are examining a 48-hour-old full-term male newborn in the nursery. The mother is only 16 years of age and did not have prenatal care because she was trying to hide the pregnancy from her parents and took no medications or supplements and had no prenatal ultrasonography. She occasionally smoked cigarettes and marijuana but stopped late in her first trimester when she learned she was pregnant. She used condoms inconsistently. Her medical history is significant for sexually transmitted infections, including gonorrhea and chlamydia, 6 months before her pregnancy. The baby is making approximately 6 wet diapers a day without any hematuria. On physical examination you note the presence of a deep sacral pit and you are unable to visualize its bottom. The muscle tone in the lower extremities is noticeably decreased. An evaluation is started. Which of the following factors most likely placed this infant at the greatest risk for possibly having this condition?
   - A. Being first born.
   - B. History of marijuana and tobacco use.
   - C. History of sexually transmitted infections.
   - D. Lack of intake of prenatal vitamins.
   - E. Maternal age.

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4. A 15-month-old boy is brought to the clinic for follow-up. He is new to the practice because the family just moved to the area. The baby was not previously seen by a primary care clinician and received no immunizations so far due to the family being uninsured. The father just started a new job in the area that provided him with insurance. Physical examination is significant for macrosomia, hemihyperplasia, and macroglossia. Further testing of the kidneys and urinary tract system is warranted because these clinical findings may be associated with which of the following conditions?

   A. Epispadias.
   B. Medullary sponge kidney.
   C. Neurogenic bladder.
   D. Renal agenesis.
   E. Renal cysts.

5. A 5-year-old boy is brought to the emergency department with a temperature of 102.2°F (39°C) and emesis for the past 24 hours. He was born at full-term and has never been diagnosed as having any medical problems. He is up-to-date on his vaccines. Physical examination reveals an ill-looking child with a pulse of 100 beats/min, blood pressure of 70/50 mm Hg, and a respiratory rate of 30 breaths/min. He has diffuse abdominal tenderness. His white blood cell count is 18,000/μL (18×10^9/L). Urinalysis shows nitrates and leukocytes. Blood and urine cultures are pending. A fluid bolus is given, and he is started on intravenous antibiotics and admitted to the hospital for hydration. Which of the following imaging studies is the most appropriate next step in assessing the cause of his symptoms?

   A. Abdominal radiography.
   B. Computed tomography of the abdomen.
   C. Intravenous pyelography.
   D. Renal ultrasonography.
   E. Voiding cystourethrography.

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Congenital Anomalies of the Kidneys, Collecting System, Bladder, and Urethra

Halima S. Janjua, Suet Kam Lam, Vedant Gupta and Sangeeta Krishna

Pediatrics in Review 2019;40;619
DOI: 10.1542/pir.2018-0242

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Ventral Abdominal Wall Defects

Sara A. Mansfield, MD, MS,* Tim Jancelewicz, MD, MA, MS*

*Division of Pediatric Surgery, Le Bonheur Children's Hospital, University of Tennessee Health Science Center, Memphis, TN

Practice Gap

Clinicians should be aware of the strategies for prenatal and postnatal management of infants with omphalocele and gastroschisis.

Objectives

After completing this article, readers should be able to:

1. Recognize the implications and differences in management between gastroschisis and omphalocele.
2. Review the initial stabilization and management of infants with omphalocele and gastroschisis.
3. Review the surgical management options and rationale for infants with ventral abdominal wall defects.

INTRODUCTION

Abdominal wall defects represent a wide spectrum of congenital anomalies. These can range from lethal limb-body wall syndrome to benign umbilical cord hernias. Gastroschisis and omphalocele are the 2 most common defects and are the focus of this review. Although both of these diseases affect the umbilical area, they differ widely in their underlying pathogenesis, genetics, and associated disorders. Consequently, their management techniques and outcomes are quite different. This article reviews the pathogenesis, genetics, diagnostics, and outcomes for each disease, followed by an in-depth review of recent management updates.

OMPHALOCELE

Pathogenesis

Omphalocele (or exomphalos) is a herniation of the abdominal viscera through a midline abdominal wall defect (Fig 1). This defect is located at the base of the umbilical stalk, and herniated viscera are covered by a 3-layer membrane of peritoneum, Wharton jelly, and amnion. This contrasts with umbilical cord hernias, which are covered by intact skin and contain only a small protrusion of abdominal contents, and gastroschisis, which has no covering at all and occurs to the right of midline (Table). Omphaloceles are present in approximately 1 per 1,100 pregnancies. However, there is a high rate of spontaneous abortion, making the incidence of omphalocele per live birth approximately 1 per 4,000 to 1 per 6,000. (1)(2)

During the fourth week of gestation, the flat embryonic disc undergoes a series of craniocaudal and lateral folding that creates a tubular, C-shaped embryo. Lateral

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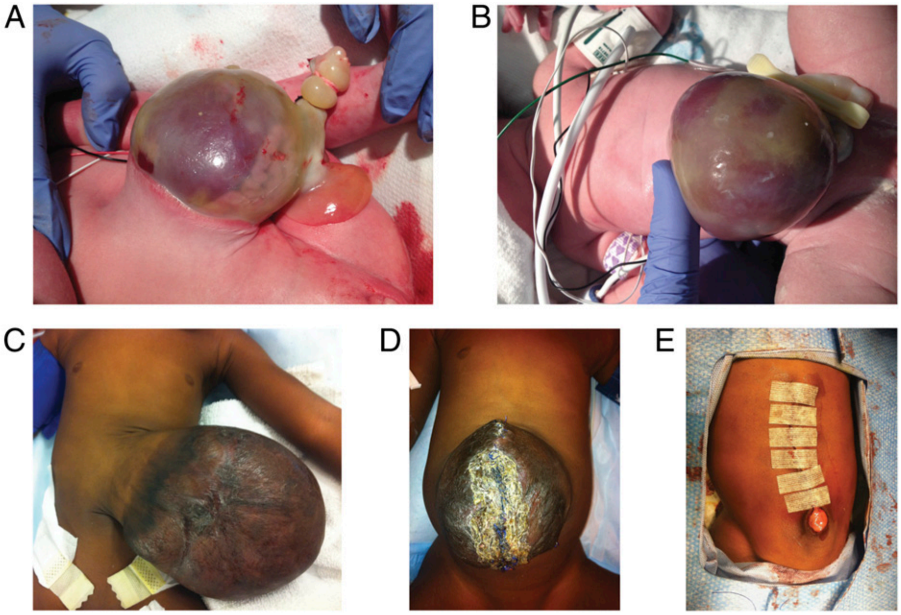

Figure 1. A. Lateral view of a newborn with an omphalocele containing liver and intestine. B. Anterior view. C. Two-year-old girl with a giant omphalocele that was completely epithelialized. The defect contained the entire liver and intestines. D. First-stage closure of a giant omphalocele, with partial reduction of contents due to lack of abdominal domain. E. Second-stage closure of a giant omphalocele, 3 months after the first stage. Primary fascial closure was achieved with this approach.

folding continues until the somatic mesoderm reaches the midline, creating the future peritoneal cavity. As the gastrointestinal tract grows rapidly, it herniates through the umbilical stalk during the sixth week of gestation due to inadequate space in the abdominal cavity. The midgut then undergoes 270° counterclockwise rotation before returning to the abdomen during gestational weeks 11 and 12. Omphalocele is thought to occur due to failure of the abdominal viscera to return to the abdomen after normal physiologic herniation. (3)

The herniated organs are variable and most commonly include the small bowel but can include others, such as the stomach, colon, bladder, and liver. (3)(4) In contrast to gastroschisis, the overlying sac protects the abdominal contents from the irritating effects of amniotic fluid exposure. With an intact sac, infants with omphalocele typically have normal gastrointestinal motility. However, ileus may be seen in the setting of a ruptured sac. The severity of the ileus is typically associated with the duration of exposure to amniotic fluid or the external environment.

Most morbidity seen in infants with omphalocele is due to associated congenital anomalies. More than 50% to 70% of infants born with omphalocele will have other congenital defects. Almost half of these infants will have a major congenital heart defect. The long-term outcomes are directly related to these other anomalies rather than to the abdominal wall defect itself. Isolated omphalocele has a survival rate of more than 95%. (5) Overall survival has been difficult to assess given the high spontaneous and elective termination rate. (6) Survival rates have been cited at less than 20% to 50% in prenatally diagnosed cases, which includes cases of termination. (1)(6)

Omphalocele is frequently seen as part of genetic disorders and syndromes. Approximately 10% of infants with

TABLE. **Defining Characteristics of Abdominal Wall Defects**

CHARACTERISTIC	OMPHALOCELE	GASTROSCHISIS	UMBILICAL HERNIA
Sac	Peritoneum, Wharton jelly, amnion	Absent	Intact skin
Location of defect	Umbilicus	Right of umbilicus	Umbilicus
Associated anomalies	Common (50%)	Uncommon (<10%)	Uncommon
Atresias	Uncommon	10%	Uncommon
Prognosis	Associated anomalies	Bowel motility	Excellent

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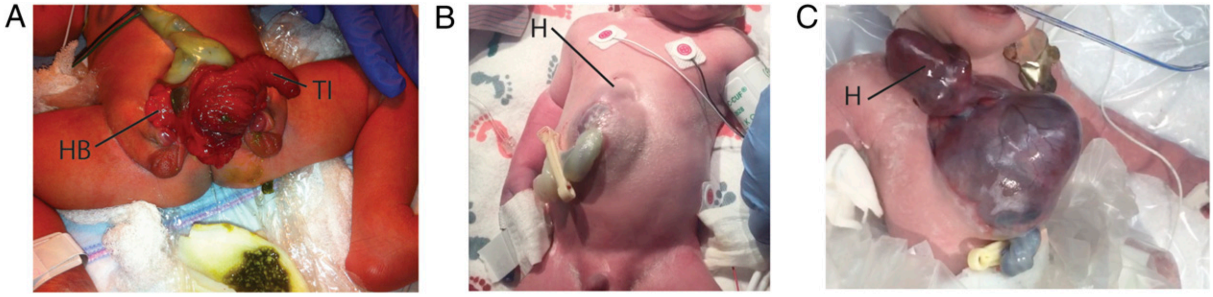


Figure 2. A. Classic cloacal exstrophy with open cecum and prolapsed terminal ileum (TI); visible is 1 hemibladder (HB). B. Pentalogy of Cantrell with epigastric omphalocele, sternal defect, anterior diaphragmatic defect, and pericardial defect, allowing the heart (H) to be visible in the epigastrium; this child was discharged from the hospital with staged repair planned at a later date. C. Complete ectopia cordis and pentalogy of Cantrell, with the heart (H) completely outside the chest; this newborn died within 24 hours of birth.

omphalocele will have Beckwith-Wiedemann syndrome (macroglossia, gigantism, omphalocele, hypoglycemia). Genetic abnormalities are identified in approximately one-third of infants with omphalocele and include trisomy 12, 18, and 21. Other conditions that result from incomplete folding of the body wall folds during embryogenesis manifest as variants of omphalocele. Infraumbilical omphalocele is often associated with genitourinary abnormalities and includes bladder or cloacal exstrophy as part of OEIS association (omphalocele, exstrophy of the bladder, imperforate anus, and spinal defects) (Fig 2A).

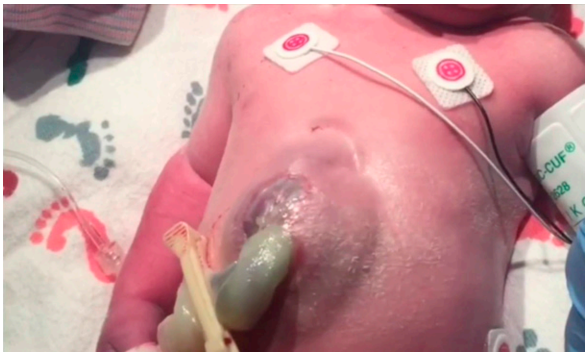
Pentalogy of Cantrell is a rare lesion (5.5 per 1 million live births) consisting of epigastric omphalocele, inferior sternal defect, anterior diaphragmatic defect, and intracardiac and pericardial defects (Fig 2B). The heart is positioned outside the thoracic space within the epigastric defect (Video 1). There is a spectrum of severity, and survival is related, in general, to the type of cardiac defect; incomplete or partial pentalogy tends toward more favorable outcomes than complete pentalogy. (7) When associated with complete ectopia cordis, survival is extremely poor (Fig 2C).

Prenatal Diagnosis and Management

Omphaloceles are usually diagnosed prenatally in the late first or second trimester. Elevated maternal serum α-fetoprotein levels should raise suspicion of an abdominal wall defect. Ultrasonography has a sensitivity of 75% to 80% and a specificity of approximately 95% for both omphalocele and gastroschisis. (1)(8) As mentioned previously, the midgut undergoes physiologic herniation during the sixth week of gestation and does not fully return to the abdomen until week 11 or 12. Therefore, a diagnosis of omphalocele should not be made before the 12th week of gestation. Karyotype analysis is indicated for all cases of suspected omphalocele. Often the prenatal diagnosis is straightforward, allowing providers to adequately counsel the patient and provide perinatal planning. However, it is important to note that prenatal imaging and karyotyping may miss 30% to 40% of associated anomalies that are subsequently found after birth. (2)

In cases in which the diagnosis is not evident, further imaging may be necessary. Fetal magnetic resonance imaging (MRI) has been advocated to better delineate anatomy, allowing for more accurate prenatal counseling. (9) Umbilical cord hernia, which has an excellent prognosis and a low likelihood of associated anomalies, can be difficult to differentiate from gastroschisis and omphalocele on conventional ultrasonography. However, in the second and third trimesters, the intact skin seen in umbilical hernias becomes apparent on MRI. If an umbilical cord hernia is present, knowledge of this finding should be communicated to delivery room staff to avoid injury to the bowel when clamping the umbilical cord.

When an omphalocele is diagnosed, prenatal evaluation should focus on identifying associated cardiac and central nervous system defects because these are the major determinants of outcome. Although ultrasonography is highly accurate at diagnosing omphalocele, (10) fetal MRI can add more information to the prediction of postnatal morbidity. (11)(12) The degree of pulmonary hypoplasia can be



Video. Pentalogy of Cantrell. The beating heart is visible under the skin due to the sternal defect, abdominal wall defect, anterior diaphragmatic defect, and absent pericardium.

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predicted by measuring the ratio between the lung and thorax transverse area. Lung volume with an observed-to-expected ratio less than 50% is associated with higher morbidity. (11)(13) In addition, the ratio of the largest diameter of the omphalocele to the head circumference can predict postnatal respiratory insufficiency, as well as the need for staged versus primary closure. (6) However, there are no prospective studies addressing these models. MRI is most valuable after 20 weeks' gestation, at a time when termination may no longer be an option. The utility of MRI seems to be in the orchestration of the advanced care needed at delivery (ie, extracorporeal membrane oxygenation). (14) MRI has not been studied regarding earlier screening and prognostic abilities.

After diagnosing an omphalocele, plans should be made for delivery at a tertiary care center with neonatology and pediatric surgical support. Full-term delivery is recommended unless earlier delivery for other obstetric indications or fetal distress is warranted. The route of delivery continues to be a topic of debate, and no study has demonstrated a benefit of cesarean delivery over vaginal delivery. Most retrospective studies have demonstrated that infants with small omphaloceles can be safely delivered vaginally. (15) Cesarean delivery should be performed only for obstetric indications. (16)(17) Some advocate for cesarean delivery of babies with giant omphaloceles due to the theoretical risk of sac rupture during vaginal delivery and the risk of hepatic trauma in infants with herniated liver. (18) There is a lack of data on the topic, and further studies are needed to make meaningful recommendations.

Postnatal Management

As mentioned previously herein, the main source of morbidity to an infant with an omphalocele is cardiopulmonary defects. Thus, the initial management of infants should include thorough cardiac and respiratory evaluation with cardiac support and intubation if necessary. Fluid resuscitation should follow because the hernia defect predisposes to large fluid losses (although less than that seen with gastroschisis). An orogastric tube should be placed for gastric decompression. The sac should be kept moist and protected with saline-soaked gauze. Infants with surgical issues such as omphalocele typically receive 48 hours of antibiotics and undergo an evaluation to rule out sepsis. Antibiotics can then be discontinued if cultures show no growth at 48 hours. Administering antibiotics may not be necessary in infants with intact omphalocele and should not be given for a long duration. (19) Once stabilized, a thorough evaluation should be performed to assess associated anomalies. This includes echocardiography, renal ultrasonography, and karyotype analysis. Definitive surgical correction is not an emergency in infants with an intact sac, allowing time for a thorough evaluation. If the sac does rupture, the infants are treated in a more urgent manner to cover the exposed viscera, similar to treating infants with gastroschisis. Enteral feeding can be started after initial stabilization in infants with unruptured omphalocele and can be safely given while awaiting definitive closure of the abdominal wall because gastrointestinal motility and function are not affected.

Surgical management of the abdominal wall defect is dictated by the size of the defect, the presence of an intact sac, and the underlying cardiopulmonary status of the infant. For small defects, primary closure should be attempted. After excising the omphalocele sac, the umbilical vessels can be ligated. The fascial edges are identified after the creation of skin flaps. After reduction of the abdominal viscera, the fascia is transversely closed. The overlying skin can be closed with a purse-string suture, recreating the umbilicus. (20)

Schuster was the first to describe the use of a silastic silo to gradually reduce the abdominal contents into the abdomen. After excising the omphalocele sac, the silo is sewn to the fascia or to the full thickness of the abdominal wall. Serial reductions are then used to return the contents to the abdomen, with the goal of fascial closure. The omphalocele sac itself can be used as a silo if the sac is free from the underlying viscera, or a silo can be placed over the sac. The sac is sequentially tightened until the viscera have reduced, allowing surgical fascial closure. Some surgeons will leave the sac intact at the time of fascial closure, known as the amnion inversion technique. (21)

Babies with significant cardiopulmonary disease may not tolerate supraphysiologic increases in abdominal pressure. For these, initial nonoperative management is preferred, with plans for delayed surgical closure. The "paint and wait" technique is a nonoperative strategy for large defects or for infants who are poor surgical candidates. (22) A thin layer of silver sulfadiazene cream is applied to the omphalocele sac and wrapped with sterile gauze. This is repeated daily until the sac is fully replaced with granulation tissue (usually 3–4 weeks). (23) Silver sulfadiazene can be applied by the parents at home, allowing the infant to be discharged from the hospital until ready for staged abdominal wall closure.

The term *giant omphalocele* is used for defects larger than 5 to 10 cm (Fig 1 C–E). There are several options for management. The Gross technique uses a bridging mesh (biologic or synthetic) with a planned hernia repair at a later date (24) or placement of a temporary vacuum dressing. (6)(25)(26) Once

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adequate abdominal wall domain is obtained, the fascia can then be closed (Fig 1E). (27) Many different techniques are performed because no single method is uniformly applicable or successful.

As discussed previously herein, the embryogenesis of abdominal wall defects includes interruption of the normal rotation of the intestines. This leads to abnormal or absent rotation of the intestines in infants with omphalocele. There is a risk of developing midgut volvulus in infants with abdominal wall defects. The risk is higher in infants with omphalocele, particularly those born with an intact sac. This is possibly due to fewer adhesions that are formed after reduction, which would normally protect the bowel from volvulus. (28) Therefore, some surgeons have recommended performing a Ladd procedure at the time of closure to decrease these risks. (29) However, other studies have not supported this practice and found that these patients are still at risk for volvulus, even with a prophylactic Ladd procedure. (30)

Outcomes

Mortality rates of omphalocele range from 15.6% to 52.4% in the neonatal period. As mentioned, survival varies depending on the presence of associated anomalies. A review from the National Birth Defects Prevention network found mortality of 28.7%, with 75% of deaths occurring within the first month. Survival was better in neonates with isolated omphalocele compared with those with chromosomal defects (hazard ratio, 7.75; 95% confidence interval, 5.4–11.1). (31) The 1-year survival of babies with isolated omphalocele is greater than 90%, compared with 27% in those with chromosomal anomalies. (32)

GASTROSCHISIS

Pathogenesis

Gastroschisis is a defect of the abdominal wall located 1 to 2 cm to the right of the umbilicus (Fig 3), and it has a very different clinical picture from an omphalocele. Gastroschisis is a herniation of the bowel without a membranous covering (Table) and is typically an isolated finding, without associated congenital anomalies. The morbidity seen in gastroschisis is directly related to the gastrointestinal dysmotility that results from exposure to amniotic fluid during gestation. Intestinal atresias are seen in approximately 6% to 28% of infants with gastroschisis. (33)(34)(35) This is thought to be due to trauma of the bowel against the abdominal wall or vascular compromise from segmental volvulus.

The incidence of gastroschisis has nearly doubled during the past few decades, with a current rate of approximately 2 to 5 per 10,000 live births. (36)(37) The most significant risk factor seems to be young maternal age, with a sevenfold

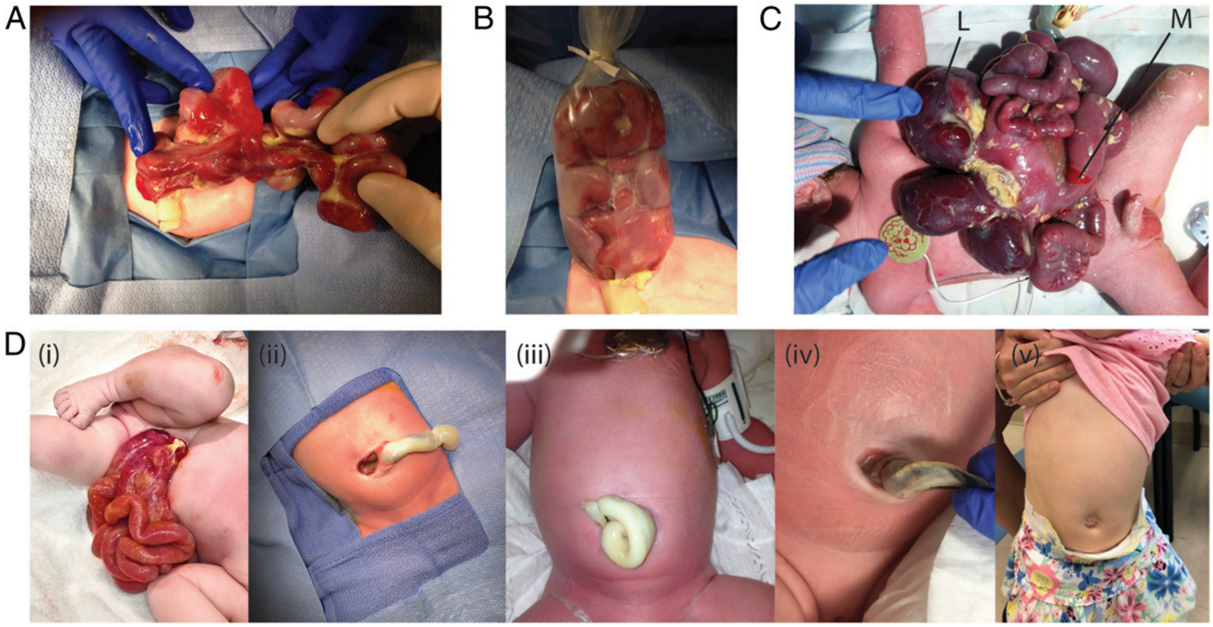

Figure 3. A. Gastroschisis with moderate bowel edema and fibrinous exudate from amniotic exposure. B. The bowel was placed into a silo to allow slow reduction over 2 to 3 days. C. Complex gastroschisis with herniated liver (L) and at least 1 intestinal atresia with visible mucosa (M); this child required very slow reduction along with stoma creation, which was very difficult due to lack of abdominal wall surface. D. Sutureless (nonoperative) closure of gastroschisis: (i) initial presentation with minimal bowel edema; (ii) successful reduction without a silo, showing the residual defect; (iii) coiling of the umbilical cord over the defect, followed by application of an occlusive dressing; (iv) appearance of the defect after 1 week of coverage; and (v) appearance of the umbilicus at 1 year of age (no umbilical hernia in this case).

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incidence among teenage mothers. Tobacco, (38)(39) recreational drug, (40) and certain decongestant (41)(42) use have also been implicated. These risk factors have been the basis for embryologic theories. The association with sympathomimetic agents such as smoking, cocaine, amphetamines, and decongestants supports a vascular accident hypothesis. Theories regarding the embryogenesis of gastroschisis include failure of lateral body wall folding, localized paraumbilical tissue weakness associated with regression of the right umbilical vein, and vascular accidents of the vitelline artery. (43)

In some cases, the abdominal wall defect may close before birth. If bowel is present in the defect, this can result in strangulation, necrosis, and possible amputation. This phenomenon is referred to as "vanishing gastroschisis." Occasionally the bowel will be seen emerging from the abdomen (Fig 4). The proximal bowel is typically dilated and dysmotile. In severe situations, a large mass of bowel is compromised and can lead to devastating short bowel syndrome. Smaller abdominal wall defects are associated with complex gastroschisis (vanishing gastroschisis, atresia, necrosis, perforation, etc). (44)

Prenatal Diagnosis and Management

Unlike omphalocele, intrauterine demise is uncommon with gastroschisis. Whereas infants with omphalocele are typically born at term, those with gastroschisis have an average gestational age of 34 to 37 weeks. (18) Gastroschisis is associated with higher maternal α-fetoprotein levels than an omphalocele (7–9 times normal versus 4 times normal). On ultrasonography, the umbilical cord insertion site is normal, but the free-floating bowel is seen outside the abdomen. The defect can be seen in a paramedian location, usually to the right of the umbilicus. Gastroschisis most commonly occurs as an isolated finding, but it is important to look for additional malformations. Approximately 10% of fetuses with gastroschisis will have an additional anomaly.

Serial ultrasonography is important to monitor bowel viability. Bowel loops may appear thickened as irritation from amniotic fluid worsens. Bowel dilation can be seen, and if severe should be a warning of an underlying atresia. Worsening dilation and echogenicity should raise the concern of threatened, ischemic bowel. Some experts recommend early delivery when signs of bowel compromise develop. Survival for infants with gastroschisis decreases to 70% if ischemia, perforation, or atresias are present at birth. A recent meta-analysis reported correlations between sonographic evidence of intra-abdominal bowel dilation and polyhydramnios with the presence of bowel atresia, as well as a correlation between gastric dilation and neonatal death. (45)

As with omphalocele, vaginal delivery is preferred unless an indication for cesarean delivery is present for obstetric reasons or fetal distress. Currently, there is no difference in outcomes between cesarean and vaginal delivery in the literature. A recent meta-analysis of available observational studies found no difference in overall mortality, ability to undergo primary repair of the abdominal wall defect, incidence of necrotizing enterocolitis, sepsis, time to full feeds, or duration of hospital stay. (46) There has been debate over the timing of delivery. Some groups advocate that preterm delivery is associated with shorter duration of exposure to amniotic fluid and, thus, less bowel dysmotility. Multiple studies, including a Cochrane review, showed no difference or higher rates of adverse outcomes associated with delivery before 36 weeks, which exposes the infant to undue risks of prematurity. (47)(48)(49) Most centers wait until the natural onset of labor.

Postnatal Management

Immediately after birth, the bowel must be protected from the environment to conserve humidity and temperature. The "bowel" bag, or Lahey bag, is the most common option. The lower half of the infant is placed into the sterile bag,

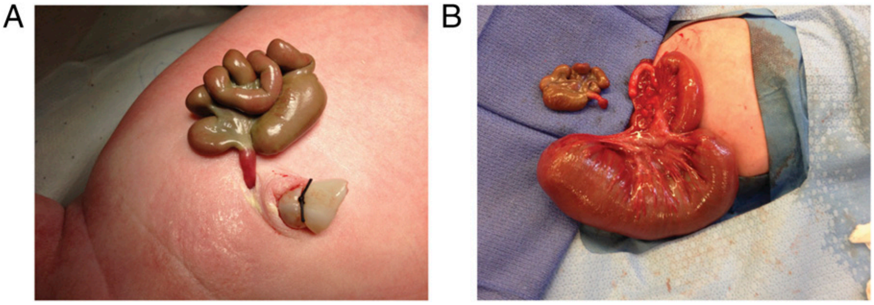

Figure 4. A. Appearance of vanishing gastroschisis at birth with infarcted intestine and a tiny residual gastroschisis defect. B. Appearance of the proximal dilated small intestine and resected infarcted segment in the same patient at laparotomy. A primary serial transverse enteroplasty procedure was performed on this patient, and she became independent of parenteral nutrition within a year of birth.

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which is then loosely tied around the chest. The bowel should be positioned in a way that protects the mesentery from twisting or kinking against the abdominal wall. The patient is laid right side down such that venous drainage from the bowel is not compromised by kinking against the fascial ridge. Judicious resuscitation is guided by vital signs, capillary refill, urine output, and acid-base status. Resuscitation with additional fluid boluses beyond that indicated by clinical parameters can lead to a need for mechanical ventilation due to pulmonary edema. (50) Intravenous access should be obtained in anticipation of starting total parenteral nutrition soon after birth.

Primary surgical closure of the defect is the preferred method if the abdomen is amenable without causing abdominal compartment syndrome. This condition occurs when there is insufficient abdominal domain to accommodate reduction of the viscera and fascial closure, leading to impaired venous return, decreased pulmonary compliance, and organ injury (renal failure, bowel ischemia). The most common closure method is suturing of the abdominal wall fascia. Most recently, a “sutureless” closure is gaining popularity. (51) With this approach, the bowel is reduced, and the umbilical cord remnant is positioned over the abdominal wall defect (Fig 3). A tight adhesive dressing is placed over this and changed every few days until the fascial defect has closed. Some infants may initially develop an umbilical hernia, but many will close over time. Sutureless closure can be performed at the bedside without general anesthesia, a benefit over sutured fascial closure; (52) there is also a lower rate of required mechanical ventilation. (53)(54) The only randomized controlled trial on the matter showed no benefit of sutureless (n=19) compared with classic sutured (n=20) closure in length of stay or time to full enteral feeding. (55)

If there is too much eviscerated bowel or if the bowel is too edematous to immediately reduce, a preformed silastic silo is placed (Fig 3B). This can be performed in the NICU. The silo is then tightened once or twice daily until the contents are fully reduced. These reductions can also be performed at the bedside with a small amount of sedation. Constant attention is given to the hemodynamics of the infant during reduction. Once fully reduced, the defect can then undergo surgical closure or sutureless closure. With any of the closure methods, the bowel should be inspected for the presence of intestinal atresias before definitive closure.

In babies with complex gastroschisis (atresia, perforation, necrosis), a bowel resection or ostomy may be required. The bowel is typically too edematous to safely repair intestinal atresias immediately at birth. Therefore, these are addressed after 4 to 6 weeks, when an anastomosis is feasible. A contrast enema is usually performed to confirm the level of the lesion(s).

The bowel is nonrotated in babies with gastroschisis. However, the degree of intestinal adhesions in these infants is usually significant enough that volvulus is a rare event. (28)

Outcomes

After surgical correction, infants with gastroschisis are still faced with significant ileus and bowel dysmotility, resulting in hospitalization for weeks to months. Total parenteral nutrition should be started soon after birth in anticipation of lack of enteral nutrition, as ileus averages 2 to 3 weeks. (43) After correction, the amount and character of the nasogastric tube output is monitored before initiation of enteral nutrition. Enteral feeds are then slowly advanced, and the infant is monitored for tolerance. Standardization of care may help with day-to-day management of these infants. (56)(57) Overall survival in infants with gastroschisis is more than 90%. Interdisciplinary intestinal failure teams should be involved to aid in long-term dysmotility management.

Summary

Omphalocele and gastroschisis are 2 of the most common congenital abdominal wall defects. The 2 disorders vary widely in presentation, embryologic origin, and management.

- Based on some research evidence as well as consensus (Level B), outcomes with omphalocele are excellent in the absence of any significant associated anomalies. (31)(32)
- There is good evidence (Level A) that survival in gastroschisis exceeds 90%, with morbidity primarily in those with intestinal injury or atresia. (45)(46)
- Based largely on mid-level evidence and a few randomized trials (Level B), there is general consensus regarding management of affected infants. (6)(17)(18)
- Based on Level B evidence, a multidisciplinary, standardized approach to treatment can lead to excellent long-term outcomes. (57)

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1. You are called to the hospital for the impending delivery of a 37-week neonate with prenatally diagnosed omphalocele. You discuss the plan with the delivery team and explain to the medical students on the team the anatomy of this condition. In your discussion, you explain that omphalocele is a herniation of the abdominal viscera through a defect in which of the following anatomical structures?
   - A. Abdominal wall.
   - B. Amnion.
   - C. Peritoneum.
   - D. Umbilical stalk.
   - E. Wharton jelly.

2. You are providing postnatal care for a term neonate with omphalocele. The baby was born at term to a 22-year-old primigravida mother who received prenatal care. Prenatal ultrasonography provided the diagnosis of abdominal wall defect along with several congenital anomalies. Pregnancy was complicated by oligohydramnios. You consult pediatric surgery and genetics. In considering the sources of greatest risk for morbidity in this patient, which one of the following factors accounts for most of the potential cause of morbidity in this patient?
   - A. Associated congenital anomalies.
   - B. Gastrointestinal dysmotility.
   - C. Irritating effects of amniotic fluid exposure.
   - D. Limited pulmonary capacity.
   - E. Young maternal age.

3. The mother of a patient in your pediatric practice is pregnant with her second child. She contacts you to get your opinion on the result of her prenatal ultrasonography, which raised concern for omphalocele. Her serum α-fetoprotein levels were elevated. Which one of the following diagnostic tests is indicated for all cases of suspected omphalocele based on ultrasonography findings?
   - A. Biophysical profile.
   - B. First trimester fetal magnetic resonance imaging.
   - C. Karyotype analysis.
   - D. Repeated serum α-fetoprotein level.
   - E. Weekly nonstress testing.

4. The mother in question 3 is at 35 weeks' gestation with a smooth pregnancy course. She is referred to the nearby tertiary care hospital, where she will be delivered by her obstetrician. The neonatology team will be present at the delivery. Which of the following is the most appropriate step to be considered in the peripartum and postnatal care of this infant?
   - A. Cesarean delivery.
   - B. Emergent definitive surgical correction at day 0 after birth.
   - C. Fluid restriction to avoid pulmonary edema.
   - D. Induction of labor at 36 weeks' gestation.
   - E. Orogastric tube placement immediately after delivery.

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5. A newborn male infant with gastroschisis is born at 37 weeks' gestation. The baby is admitted to the NICU where he is stabilized. Surgical correction is planned in the next few weeks. The family asks how long they should anticipate their baby to remain in the hospital after surgical correction. Which of the following best describes the expected inpatient stay after surgical correction for gastroschisis in this patient?

   A. At least 72 hours, until oral feeds are tolerated.
   B. On average 10 days, until an antibiotics course is completed.
   C. Several days postoperatively, until the first bowel movement.
   D. Up to 3 weeks, until weight gain is established.
   E. Weeks to months, due to significant dysmotility.

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Ventral Abdominal Wall Defects

Sara A. Mansfield and Tim Jancelewicz

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Index of Suspicion

1 Abdominal Distention in a 2-month-old Boy

Diana Haddad, MD,* Sandeep Gangadharan, MD†

*Department of Pediatric Critical Care Medicine, Cohen Children's Medical Center, New Hyde Park, NY

†Department of Pediatric Critical Care Medicine, Children's Hospital at Montefiore, Bronx, NY

EDITOR'S NOTE

Has 2019 been perfect? Even amidst good times, we often face challenges. Some of the challenges are because we battle structures and systems that just weren't made perfectly, and sometimes we face challenges of imperfect processes. This month, the *Index of Suspicion* cases (and some of the other articles in this issue) deal with structural and biochemical (process) problems. Enjoy!

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A 2-month-old full-term boy with normal prenatal ultrasonography findings and an unremarkable birth history presents to the emergency department with several days of forceful, nonbloody, nonbilious vomiting and worsening abdominal distention. His oral intake and urine output are decreased. His history is significant for gastroesophageal reflux, but he is developing well.

On examination he appears ill. His vital signs are significant for hypertension (blood pressure, 160/90 mm Hg) and tachypnea with shallow breathing. He has a distended abdomen and mottled extremities. The physical examination findings are otherwise normal. He has not had fevers, rash, swelling, or changes in his stools.

An abdominal radiograph reveals no evidence of obstruction or intraperitoneal free air. Ultrasonography of the abdomen shows moderate ascites. There is no pyloric stenosis. The liver and spleen are normal in size. There is mild hydronephrosis of the left kidney and a large subcapsular collection that is compressing the renal parenchyma. The bladder wall appears thickened.

His complete blood cell count shows a platelet count of $924\times10^3/\mu L$ ($924\times10^9/L$). A complete metabolic panel shows a low sodium level of 125 mEq/L (125 mmol/L), an elevated potassium level of 6.9 mEq/L (6.9 mmol/L), a blood urea nitrogen level of 44 mg/dL (15.7 mmol/L), and a creatinine level of 1.5 mg/dL (132.6 μmol/L). Findings from liver function tests and urinalysis are normal. He is admitted to the PICU for monitoring and further management of his renal failure.

On arrival at the PICU he is intubated for worsening respiratory distress. A paracentesis drain is placed, and ascites fluid is sent for analysis, which leads to the diagnosis.

AUTHOR DISCLOSURE Drs Haddad and Gangadharan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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TABLE 1. **Differential Diagnoses for Ascites**

ETIOLOGY OF ASCITES	SUGGESTED LABORATORY TESTING OF ASCITIC FLUID
Congestive hepatopathy (cirrhotic and noncirrhotic, including heart failure)	Albumin (to calculate serum-to-ascites albumin gradient)
Peritoneal infection or inflammation	Culture and cell count with differential count
Biliary or pancreatic ascites (traumatic or nontraumatic)	Bilirubin, lipase, and amylase levels
Genitourinary disorders (ie, obstructive uropathy)	Creatinine +/- urea levels
Chylous ascites	Triglyceride level and cell count with differential count
Malignancy	Protein, cytology, and tumor markers

DISCUSSION

Biochemical analysis of the clear yellow peritoneal fluid suggested that it was a transudate. The fluid creatinine level was moderately elevated, suggesting that the fluid was urinary in origin. Urinary ascites should be considered after more common causes of transudative ascites have been ruled out. In this case, there was no hepatomegaly noted on ultrasonography, lessening the likelihood of suprahepatic obstruction (Budd-Chiari syndrome), cardiac issues, or storage disease. Nephrotic syndrome must also be considered, but this patient had no proteinuria.

An ascites creatinine to serum creatinine ratio greater than 1.0 is highly suggestive of an intraperitoneal urine leak, whereby urine accumulates as free fluid in the peritoneal cavity. The most common cause of urinary ascites in neonates is congenital obstructive uropathy. Downstream obstruction causes increased pressure in the kidney, which leads to the perinephric extravasation of urine. This is compared with acquired cases that occur later in life usually due to complications of pelvic surgery if the bladder or ureters are inadvertently injured.

A urology consult was obtained and the patient was sent for a voiding cystourethrogram, which showed a dilated posterior urethra, spontaneous vesicoureteral reflux into a tortuous and dilated left ureter, hydronephrosis, and subsequent visualization of contrast in the subcapsular collection on the left, likely from a lower pole fornix. These findings confirmed a diagnosis of posterior urethral valves. There was unilateral high-grade vesicoureteral reflux, with fornix rupture and a large perinephric urinoma that had also ruptured, causing urine to leak into the peritoneum.

The Condition

Posterior urethral valves are congenitally occurring membranous folds located in the posterior urethra that obstruct the outflow of urine from the bladder. They are the most common etiology of bladder outlet obstruction in male newborns. The bladder responds to the increased resistance by detrusor muscle hypertrophy, which leads to vesicoureteric incompetence or obstruction that causes reflux and hydroureteronephrosis. The back pressure of urine in the renal collecting system may find a "pop-off" into the perinephric space.

This pop-off mechanism seems to initially protect the kidneys from the deleterious effects of elevated bladder pressures. However, with time the extrinsic renal compression from the urinoma can decrease perfusion to the compressed kidney, which causes hypertension and loss of renal function, a condition known as Page kidney. There are higher concentrations of creatinine and potassium in urinary ascites than in serum. These substances then diffuse into the blood, making the renal failure seem even worse.

Management

The patient's creatinine concentration improved to baseline with slow drainage of the urinary ascites. On the third hospital day, he underwent a successful primary valve ablation via cystoscopy. The vesicoureteral reflux resolved, his kidney function improved, and his electrolytes normalized. He was discharged from the hospital on 1 medication for hypertension, which was later discontinued, and he is currently thriving.

Lessons for the Clinician

- Urinary ascites should be considered in the broad differential diagnosis of ascites, when more common causes

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have been ruled out (Table 1). Laboratory testing of ascitic fluid should be performed along with other clinical investigations, such as a thorough history, physical examination, and possible imaging, in the evaluation of infants presenting with abdominal distention and ascites.

- The most common cause of urinary ascites in neonates is congenital obstructive uropathy, which causes increased pressure in the kidney that may "pop-off," leading to the perinephric extravasation of urine. Posterior urethral valve (PUV) is the most common cause of obstructive uropathy in male infants.
- The presence of PUV may be suggested prenatally by ultrasonography findings. Bladder outlet obstruction can lead to distention of the bladder and proximal urethra (the "keyhole" sign) that could suggest the presence of PUV, but these findings may also be absent either because the obstruction is mild or because routine anatomy ultrasonography is performed too early in gestation (18–22 weeks). Hydronephrosis may or may not be present. Oligohydramnios is a late finding in severe cases.
- Patients, thus, often present postnatally with abdominal distention due to urinary ascites, but the condition should also be suspected in male infants with decreased urine output or difficulty voiding. PUV is diagnosed by voiding cystourethrogram, and the treatment is surgical ablation of obstructing valves.

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Case 1: Abdominal Distention in a 2-month-old Boy

Diana Haddad and Sandeep Gangadharan

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Index of Suspicion

2 A 2-month-old Girl with Liver Failure and a Brother with Tyrosinemia Type I

Galit Tal, MD,* Dalit E. Dar, PhD,† Shlomo Almashanu, PhD,‡
Stanley H. Korman, MBBS,* Elena Dumin, MD, PhD†§

*Metabolic Unit, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa, Israel
†Department of Clinical Biochemistry, Rambam Health Care Campus, Haifa, Israel
‡National Newborn Screening Program, Ministry of Health, Tel HaShomer, Israel
§Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

PRESENTATION

A 2-month-old girl presents with jaundice, pallor, and abdominal distention. She was born by normal delivery at term weighing 2,380 g. Her 22-month-old brother has tyrosinemia type I detected on newborn screening (NBS) and subsequently confirmed by the presence of succinylacetone on a urine organic acid analysis and demonstration of homozygosity for the IVS8-1(g-c) mutation in the *FAH* gene. He is doing well and has normal liver function on standard treatment with NTBC (nitisinone) and a tyrosine- and phenylalanine-restricted diet. The parents are first cousins of Christian Arab origin from the north of Israel and confirmed to be heterozygous for the *FAH* mutation. Prenatal genetic diagnosis performed in the latest pregnancy on chorionic villus sampling indicated that the girl is a heterozygous carrier for the *FAH* mutation. Findings from her NBS were completely normal, including a negative test for succinylacetone. She is being bottle-fed with a regular infant formula.

On examination she looks pale and sweaty, although alert. Her abdomen is swollen but not tender, with a firm liver edge palpable below the costal margin, spleen not palpable. Initial laboratory results (Table) reveal a blood sugar level of 34 mg/dL (1.9 mmol/L), elevated hepatocellular and cholestatic liver enzyme levels, direct hyperbilirubinemia, hypoalbuminemia, and abnormal coagulation studies consistent with synthetic liver failure. She is treated with a glucose infusion and intramuscular vitamin K. In light of the family history and her presentation with synthetic liver failure, tyrosinemia type I is highly suspected despite the negative prenatal genetic testing and NBS. Urine organic acid analysis, indeed, reveals increased excretion of tyrosine metabolites, but succinylacetone is not detected. The results of her plasma amino acid profile (Table) suggest a different diagnosis.

DISCUSSION

Differential Diagnosis

Inborn errors of metabolism (IEMs) are an important cause of liver failure in neonates and young infants. (1) Many IEMs are treatable, including disorders of carbohydrate metabolism, such as galactosemia and hereditary fructose intolerance; disorders of amino acid metabolism and transport, such as tyrosinemia type

AUTHOR DISCLOSURE Drs Tal, Dar, Almashanu, Korman, and Dumin have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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TABLE. **Laboratory Results**

TEST	PRETREATMENT	ON DIET 4 DAYS	ON DIET 2 MONTHS	REFERENCE RANGE
Glucose, mg/dL (mmol/L)	34 (1.9)	61 (3.4)	76 (4.2)	70–99 (3.9–5.5)
AST, U/L (μkat/L)	148 (2.47)	90 (1.50)	79 (1.32)	5–34 (0.08–0.57)
ALT, U/L (μkat/L)	63 (1.05)	45 (0.75)	59 (0.99)	0–55 (0–0.92)
GGT, U/L (μkat/L)	560 (9.35)	617 (10.30)	140 (2.34)	9–36 (0.15–0.60)
Bilirubin, total, mg/dL (μmol/L)	6.10 (104)	2.27 (38.8)	0.64 (11.0)	0.2–1.2 (3.42–20.5)
Bilirubin, direct, mg/dL (μmol/L)	4.39 (75.1)	1.55 (26.5)	0.36 (6.16)	0–0.5 (0–8.55)
Albumin, g/dL (g/L)	2.8 (28)	2.9 (29)	4.1 (41)	3.8–5.4
Total protein, g/dL (g/L)	4.8 (48)	4.5 (45)	6.1 (61)	6.4–8.3
INR	1.52	0.85		0.8–1.2
APTT, sec	52.4			25–41
α_1-Fetoprotein, ng/mL (μg/L)	85,740 (85,740)[a]		924 (924)[bc]	[ab]
Fibrinogen, mg/dL (g/L)	147 (1.47)			157–360 (1.57–3.60)
Amino acids, mg/dL (μmol/L)				
Citrulline	6.03 (344)	0.65 (37)	0.26 (15)	0.11–0.88 (6–50)
Tyrosine	7.12 (393)	2.23 (123)	1.09 (60)	0.18–3.62 (10–200)
Phenylalanine	1.85 (112)	0.91 (55)	0.73 (44)	0.50–2.15 (30–130)
Methionine	8.45 (566)	8.42 (564)	0.36 (24)	0.22–0.97 (15–65)
Arginine	8.22 (469)	3.93 (224)	1.75 (100)	0.21–2.80 (12–160)
Lysine	8.13 (556)	7.03 (481)	2.50 (171)	1.46–5.26 (100–360)
Threonine	7.00 (588)	3.87 (325)	2.48 (208)	0.71–4.29 (60-360)
Serine	2.85 (239)	2.87 (241)	1.54 (129)	0.63–3.15 (60-300)
Threonine-to-serine ratio	2.46	1.35	1.61	≤1.5
Glutamine	3.10 (212)	7.5 (513)	9.11 (623)	5.70–14.6 (390–1,000)

ALT=alanine aminotransferase, APTT=activated partial thromboplastin time, AST=aspartate aminotransferase, GGT=γ-glutamyltransferase, INR=international normalized ratio.

[a] *α_1-Fetoprotein reference intervals for age 1 to younger than 3 months: 10 to 1,359 ng/mL (10–1,359 μg/L).*

[b] *α_1-Fetoprotein reference intervals for age 3 to younger than 6 months: 4 to 275 ng/mL (4–275 μg/L).*

[c] *α_1-Fetoprotein was 30 ng/mL (30 μg/L) after 6 months of treatment.*

I; the urea cycle disorders, including citrin deficiency; and fatty acid oxidation disorders. Other IEMs to consider include mitochondrial respiratory chain disorders, congenital disorders of glycosylation, transaldolase deficiency, and Niemann-Pick type C disease. In this patient, tyrosinemia type I was suspected because of the history of an affected sibling but was unlikely in view of the negative testing for succinylacetone. Nevertheless, rare cases of tyrosinemia type I with undetectable succinylacetone have been reported. (2) Particularly in the context of parental consanguinity, the possibility of a second IEM in the same family also needs to be considered.

Actual Diagnosis

Plasma amino acid analysis revealed elevated citrulline, arginine, threonine, lysine, and methionine levels; low glutamine levels; and an elevated threonine-to-serine ratio (Table). α_1-Fetoprotein level was markedly elevated. These findings were highly suggestive of citrullinemia type II, also known as citrin deficiency. Sequencing of the citrin-encoding gene *SLC25A13* revealed a novel homozygous c.848G>T p.G283V mutation predicted to be pathogenic.

The Condition

Citrin, an aspartate-glutamate mitochondrial inner membrane transporter, is defective in citrullinemia type II. Citrin is essential

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for normal functioning of the urea cycle by providing aspartate for the synthesis of argininosuccinic acid (Fig). Citrin is also an important component of the malate-aspartate transporter, which transports cytosolic NADH from glycolysis into the mitochondria. Carbohydrate ingestion causes an increase in the cytosolic NADH/NAD$^+$ ratio, which inhibits aerobic glycolysis in cells, leading to energy shortage in hepatocytes and suppression of ureogenesis. Furthermore, increased NADH also impairs galactose metabolism, leading to accumulation of other toxic compounds in hepatocytes, similar to galactosemia.

The clinical phenotype of citrin deficiency varies according to the age at onset. (3) The neonatal/infantile form presents with transient intrahepatic cholestatic hepatitis, whereas the late adolescence or adult form presents with neuropsychiatric symptoms associated with hyperammonemia. In the intervening period, affected children may be apparently asymptomatic but have failure to thrive, dyslipidemia, fatty liver, and aversion to carbohydrates. (4)

Infants may present with prolonged cholestatic jaundice and failure to thrive, accompanied by hypoalbuminemia, abnormal coagulation profile, liver dysfunction, hypoglycemia, hemolytic anemia, and hypergalactosemia. The plasma amino acid profile shows elevation of not only citrulline but also arginine, methionine, tyrosine, and threonine levels, with an elevated threonine-to-serine ratio. Citrin deficiency might be detected on NBS by elevation of any of the previously mentioned amino acids or as a false-positive for galactosemia screening. However, only approximately 40% of infants with citrin deficiency have an abnormal NBS result. (5) In Israel the proportion is likely to be even lower because galactosemia is not included in the national NBS program. Diagnosis is confirmed by mutation analysis of the *SLC25A13* gene.

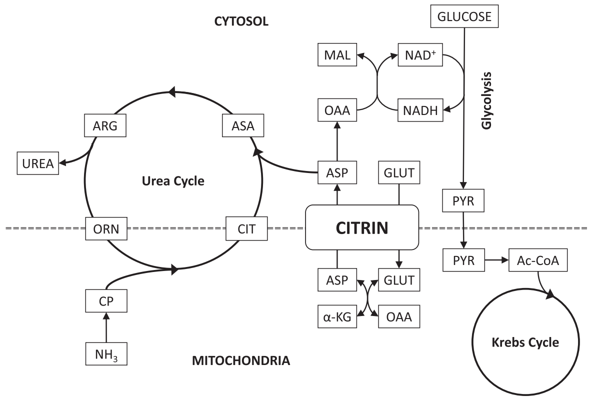

Figure. Role of citrin, an aspartate glutamate carrier, located on the inner mitochondrial membrane of the hepatocytes, involved in ureogenesis by supplying aspartate for the formation of argininosuccinic acid in the urea cycle and an important component of the malate-aspartate transporter, which transports cytosolic NADH from glycolysis into the mitochondria. α-KG=alpha-ketoglutarate, Ac-CoA=acetyl-CoA, ARG=arginine, ASA=argininosuccinic acid, ASP=aspartate, CIT=citrulline, CP=carbamoyl phosphate, GLUT=glutamate, MAL=malate, NH$_3$=ammonia, OAA=oxaloacetate, ORN=ornithine, PYR=pyruvate.

Treatment/Management

Treatment with a lactose-free formula, as in galactosemia, and provision of medium-chain triglycerides (MCTs) as an alternative source of energy to the hepatocytes should be initiated as soon as the diagnosis of citrin deficiency is suspected in cholestatic infants. (6) After the first year of life, a low-carbohydrate, high-protein, and high-fat diet, as preferred by the patients, is recommended. Administration of arginine, sodium pyruvate, and/or MCTs may be beneficial. Liver transplant may be required to prevent the hyperammonemic episodes and correct the metabolic disturbances. (7)

Patient Course

Once citrin deficiency was suspected, glucose infusion was ceased and she was started on a lactose-free formula enriched with additional MCTs. Repeated blood tests showed improvement in hepatocellular and cholestatic liver enzyme levels and blood albumin levels, resolution of her direct hyperbilirubinemia, and normalization of her coagulation studies (Table). She maintained normoglycemia when fed every 3 hours. She was discharged from the hospital after 5 days in good general condition. She is now 7 months of age and continues regular follow-up in the Metabolic Clinic. She has mild global developmental delay and hypotonia. Her weight and height are between the 5th and 10th percentiles for age.

Lessons for the Clinician

- Two different rare inherited inborn errors of metabolism (IEMs) with overlapping phenotypes may occur in the same family, particularly if there is parental consanguinity, leading to diagnostic confusion.
- Prompt recognition and accurate diagnosis of treatable IEM causing liver disease in infancy is crucial for initiation of early lifesaving treatment.
- Citrin deficiency presents in neonates or young infants as intrahepatic cholestasis with low birthweight, hepatomegaly, liver dysfunction, hypoproteinemia, coagulopathy, and/or hypoglycemia.
- The characteristic laboratory findings include an amino acid profile with elevated citrulline, methionine, arginine, tyrosine, and phenylalanine levels, together with galactosemia and markedly elevated α-fetoprotein.
- Whereas patients with citrullinemia type I and other urea cycle disorders require a low-protein, high-carbohydrate diet, patients with citrullinemia type II develop an

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aversion to carbohydrates and respond to a diet high in protein and fat and low in carbohydrates.

- Citrin deficiency may be detected by newborn screening (NBS), but only in a minority of cases. Clinicians need to be aware of the disorders included in their regional NBS program and the limitations in detection of tyrosinemia type I and citrin deficiency by NBS.

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Index of Suspicion

3

Persistent Elevated Transaminase Levels in a 9-year-old Boy

Diane Hsu, MD,* Rohit Josyabhatla, MD,* Iona M. Monteiro, MD*

*Department of Pediatrics, Rutgers New Jersey Medical School, Newark, NJ

PRESENTATION

A 9-year-old overweight boy with seasonal allergies is referred to our gastroenterology service for persistently elevated transaminase levels for 6 months. His aspartate aminotransferase (AST) level is 90 U/L (1.5 μkat/L) and alanine aminotransferase (ALT) level is 103 U/L (1.7 μkat/L). In addition, he has an elevated cholesterol level (243 mg/dL [6.3 mmol/L]), a low high-density lipoprotein (HDL) cholesterol level (36 mg/dL [0.9 mmol/L]), and a borderline high triglyceride level (151 mg/dL [1.7 mmol/L]). On presentation he notes pain in the right upper quadrant that is dull, 5 of 10 in severity, and without aggravating or relieving factors. He recently had 3 loose, nonbloody, nonmucoid stools. He denies nausea, vomiting, chest pain, lower back pain, urinary frequency, or dysuria. His diet is rich in processed foods. His physical activity is minimal. He has no home medications or family history of liver disease. However, his 38-year-old father has an elevated cholesterol level and hypertension.

His BMI is between the 90th and 95th percentiles for age. His physical examination is significant for right and left upper quadrant tenderness on deep palpation without guarding or rigidity. He has no hepatosplenomegaly. Diet and exercise counseling is provided. The repeated transaminase levels are still elevated. Iron studies and ceruloplasmin levels are normal, and hepatitis panel, anti–smooth muscle/mitochondrial antibodies, liver-kidney microsomal antibody, α1-antitrypsin phenotype, and antinuclear antibodies are all negative. Abdominal ultrasonography shows mild splenomegaly.

During his follow-up visit, the patient notes epigastric pain and intermittent loose stools. His celiac panel is negative, and his transaminase and lipid levels are persistently elevated (AST, 69 U/L [1.2 μkat/L]; ALT, 100 U/L [1.7 μkat/L]; cholesterol, 236 mg/dL [6.1 mmol/L]; HDL cholesterol, 32 mg/dL [0.8 mmol/L]; and triglycerides, 226 mg/dL [2.6 mmol/L]). Complete blood cell count and results of coagulation studies are normal. Despite diet and exercise, he has gained 5 kg. Compliance with lifestyle modifications is emphasized. Due to lack of specific etiology, the decision is made to perform a liver biopsy, which reveals the diagnosis.

DISCUSSION

Patient Course

The liver biopsy showed multiple macrophages filled with delicate material that stained positive for CD68, consistent with Niemann-Pick disease (NPD). Four

AUTHOR DISCLOSURE Drs Hsu and Josyabhatla have disclosed no financial relationships relevant to this article. Dr Monteiro has disclosed that she is a site investigator for Allergan Inc for an investigational drug for constipation. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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months later his abdominal pain improved but his transaminase, cholesterol, and triglyceride levels remained elevated. Genetic testing showed he was heterozygous for both the p.Q10X mutation and the p.W353L variant in the sphingomyelin phosphodiesterase 1 gene and had reduced sphingomyelinase activity, confirming the diagnosis. His parents and siblings are all carriers.

During a follow-up visit, he started to complain of shortness of breath. Chest radiography showed ground-glass opacities in both lung bases, consistent with interstitial disease. A computed tomographic scan of the chest was performed, which showed a diffuse miliary nodular pattern of interstitial disease with bibasilar predominance, consistent with NPD type B. The patient was seen by ophthalmology and neurology, and ocular and neurologic abnormalities were not identified, respectively. He is currently being managed with lifestyle modifications and close follow-up.

Differential Diagnosis and Evaluation

The differential diagnosis for children with elevated transaminase levels is very broad. This case raised a few important questions regarding the upper limit of normal for transaminase levels, screening for nonalcoholic fatty liver disease (NAFLD), and the approach for children with chronically elevated transaminase levels.

Elevated transaminase levels in an asymptomatic child are a common occurrence in the pediatric population, and researchers have proposed that current thresholds for transaminases should be lowered to improve sensitivity. Whereas AST is present in the cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung, leukocytes, and erythrocytes, ALT is a more specific marker of liver damage. Researchers questioned the upper limit of normal for ALT levels because the median upper limit of normal of ALT levels at children's hospitals was 53 U/L (0.89 μkat/L). (1) The Screening ALT for Elevation in Today's Youth study examined healthy adolescents and highlighted that the threshold for ALT levels was too high to detect chronic liver diseases such as hepatitis B, hepatitis C, and NAFLD because the threshold had a low sensitivity of 30% to 40%. Despite being freestanding children's hospitals, most children's hospitals in the United States are not using sex-specific thresholds for ALT levels, leading to wide variability among hospitals. When the National Health and Nutrition Examination Survey used sex-specific ALT thresholds of 25.8 U/L (0.43 μkat/L) for boys and 22.1 U/L (0.37 μkat/L) for girls, the sensitivity for detecting chronic liver disease doubled with only a minor reduction in specificity.

In this case, there was a high index of suspicion for NAFLD because the patient had risk factors such as being overweight, being male, and having dyslipidemia with a low HDL cholesterol level. Current North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines state that there is no optimal age to start screening for NAFLD because there is a lack of pediatric studies on the incidence and disease progression. (2) However, NASPGHAN recognizes that screening high-risk patients is important because lifestyle changes, such as a healthy diet and exercise, can reverse NAFLD before it leads to advanced fibrosis. ALT can be used for screening because other methods, such as ultrasonography, magnetic resonance imaging, and computed tomography, are unreliable, are costly, and have increased radiation exposure, respectively. However, children with NAFLD can still have steatosis on ultrasonography even if they have a normal ALT level. Liver biopsy remains the gold standard for diagnosis, although there is no consensus on the optimal timing for biopsy.

The approach to a child with elevated transaminase levels is debatable. A fluctuating pattern for elevated transaminase levels is common; therefore, retesting is recommended. In a retrospective study, researchers concluded that the elevated transaminase levels in healthy children were mostly benign, and liver biopsy provides minimal contribution. (3) Others have favored a more aggressive approach to evaluating abnormal transaminase levels because chronically elevated transaminase levels can suggest an underlying liver disorder. (4) In diseases such as hepatitis B, autoimmune hepatitis, NAFLD, and Wilson disease, early detection can lead to favorable outcomes and prevent progression to fibrosis and cirrhosis. (5)(6)(7)(8) Two retrospective studies found that 9% to 12% of isolated elevations in transaminase levels were due to genetic disease. (5)(9) Patients with inborn errors of metabolism and congenital disorders involving the liver can be asymptomatic and may be underdiagnosed if evaluation is inadequate. (10)

Currently, there is no standard diagnostic algorithm but there are several approaches to elevated transaminase levels based on literature review and expert opinion. (4)(6)(10) An initial evaluation should include a thorough history and physical examination. The history should include an investigation of symptoms, drug ingestion, risk factors for viral hepatitis, autoimmune or metabolic disorders, and consanguinity. Duchenne and Becker muscular dystrophies can also present as isolated elevated transaminase levels and should be ruled out. (11)

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The timing of retesting remains a question. Before repeated laboratory testing, the patient should temporarily discontinue hepatotoxic medications and limit exercise, which can lead to elevated transaminase levels. AST and ALT measurements should be repeated, along with γ-glutamyl transferase and creatine phosphokinase, because patients can have spontaneous normalization of transaminase levels ranging from 26% to 73.6%. (5)(9) γ-Glutamyl transferase rather than alkaline phosphatase values are more useful to differentiate hepatocellular from cholestatic causes (10). Viral markers of infection, hypothyroidism, endocrine disorders, autoimmune hepatitis, Wilson disease, hemolytic disorders, and metabolic disorders are also part of tier 1 or 2 of the evaluation. Further investigation includes ultrasonography of the liver and biliary tree to rule out acute obstruction.

Liver biopsy is generally reserved for cases when enzymes and other noninvasive diagnostic tests are inconclusive but can be an essential tool to distinguish among hepatitis, cholestasis, steatosis, infectious disease, and storage or infiltrative disease and aid in prognosis. (12) Evaluation using liver biopsy has been better studied in adults with elevated transaminase levels, but even in adults, the utility of liver biopsies in changing diagnosis and management has been variable. (13)(14) According to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, the indications for liver biopsy are evolving as other less invasive measures can replace biopsy in some situations. (15) However, liver biopsy remains the standard for obtaining histopathologic markers for metabolic conditions and can be used to assess the severity and progression of liver disease.

In this case, our patient had an extensive evaluation before his diagnosis and raises the question regarding the cost-effectiveness of his evaluation. Although mild splenomegaly was picked up on initial ultrasonography, the cause was attributed to a primary liver pathology given the persistently elevated transaminase levels. Mild splenomegaly in the pediatric population is most often due to a viral infection (Epstein-Barr virus, cytomegalovirus, or human immunodeficiency virus). Other important causes of splenomegaly broadly include hematologic disorders, infiltrative disorders, congestive splenomegaly, and chronic inflammatory diseases. However, given the paucity of his symptoms, normal blood cell counts, and lack of splenomegaly on initial and subsequent physical examinations, the focus remained on his elevated transaminase levels. The authors speculate whether the chest radiograph could have served as a simple screening test. The finding of interstitial lung disease might have then changed the approach in the context of mild splenomegaly and elevated transaminase levels in an overweight child, and acid sphingomyelinase assay may have then preceded a more invasive test such as a liver biopsy. However, a chest radiograph was not obtained initially because he did not have respiratory symptoms at presentation.

Actual Diagnosis

NPD is a rare genetic disorder that encompasses a family of diseases, including primary acid sphinomyelinase deficiency (types A and B) and an endosomal-lysosomal trafficking disorder (type C). (16)(17) Types A and B are caused by mutations in the sphingomyelin phosphodiesterase 1 gene *(SMPD1)*, which results in deficient activity of acid sphingomyelinase and subsequent accumulation of sphingomyelin in the central nervous system and nonneural tissue. (18) Patients with type A NPD are healthy at birth but develop hepatosplenomegaly, lymphadenopathy, and motor delays by 6 months of age, followed by regression and death by age 3 years. Type B NPD typically presents with hepatosplenomegaly, thrombocytopenia, delayed skeletal maturation, interstitial lung disease, hyperlipidemia, and ocular changes without neurologic involvement. (18)(19)(20)(21) Type C NPD is caused by mutations in *NPC1* and *NPC2* genes, resulting in lipid accumulation in lysosomes. (17) Type C can have a range of presentations from a fatal progressive disease starting from infancy to a neurodegenerative disease in adulthood. The diagnostic approach to NPD depends on the suspected subtype.

Type A and B NPD are diagnosed by acid sphingomyelinase deficiency and mutations in the *SMPD1* gene. Diagnosis of type C NPD has undergone recent changes. Filipin stain positivity in cultured fibroblasts or mutations in *NPC1* or *NPC2* genes used to be first line. They have been replaced by an assay of plasma oxysterols, a simple and rapid screening test. If the biomarkers are suspicious for NPD, the diagnosis can be confirmed with *NPC1* and *NPC2* sequencing.

Treatment/Management

Currently, there is no recommended definitive treatment for NPD, and supportive measures are encouraged. (16) Type A NPD should have physical and occupational therapy and nutrition monitoring to assess their growth. Type B NPD should have routine follow-up every 6 to 12 months to assess growth, nutrition, bleeding, shortness of breath, and abdominal pain. Although there is no approved treatment for type B NPD, research is currently being conducted with enzyme therapy and gene splicing therapy. (22)(23) Miglustat, an inhibitor of glycosphingolipid synthesis,

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has been approved for the treatment of type C NPD in Europe.

Lessons for the Clinician

- Niemann-Pick disease is a genetic disorder that should be considered in a child with abdominal pain and persistently elevated transaminase levels.
- The evaluation of children with elevated transaminase levels lacks standardization. The definition of elevated transaminase levels should better reflect the age- and sex-based norms for healthy children.
- Future studies should be directed toward the development and evaluation of a systematic approach to elevated transaminase levels because early detection may improve prognosis.
- The necessity of performing a liver biopsy remains controversial and a consensus regarding the timing and utility of liver biopsy has yet to be reached.

Note: This case is based on a poster presentation by Drs I.M. Monteiro and W. Attia at the Annual Meeting of the North American Society for Pediatric Gastroenterology and Nutrition, Washington, DC, October 8, 2015. Poster No. 488.

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4

Chronic and Progressive Muscle Weakness in a 9-year-old Girl

Aaron Powell, MD,* Pamela Wilson, MD,* Tamara Powell, PhD*

Department of Rehabilitation, Children's Hospital Colorado, Aurora, CO

PRESENTATION

A 9-year-old previously healthy girl presents to the clinic with complaints of progressive weakness during the past 2 years. She recently quit her swim and dance teams because her weakness is so severe that she cannot keep up with her peers. She noticed more difficulty with tasks such as opening jars and exhibited decreased endurance for all physical activity. Other notable symptoms include difficulty initiating and sustaining sleep, as well as weight loss despite increasing calorie consumption. She denies diplopia, muscle twitching or cramping, numbness or tingling in her limbs, bowel or bladder changes, or difficulties with swallowing. She does not have a family history of neuromuscular disease.

Vital signs reveal slight tachycardia. Examination reveals a thin young girl in no apparent distress. She has no obvious facial or shoulder girdle muscle wasting. Strength is diffusely 4/5 throughout her upper and lower limbs. Coordination and motor planning tasks are within normal limits. A Gowers sign is negative. Her gait is essentially normal, with a small increase in foot slap during initial contact after prolonged walking.

Evaluation includes screening laboratory values of creatine kinase, complete blood cell count, thyrotropin, and free thyroxine (T4). All laboratory values return normal except for thyrotropin (which was undetectable) and free T4 (which was 15.1 ng/dL [194.3 pmol/L]).

DISCUSSION

Clinical Assessment of Muscle Weakness

The assessment of weakness in the child can be daunting because the differential diagnosis is broad. However, a thorough history, physical examination, and basic laboratory work can help to narrow the list of potential diagnoses. Although some diagnoses require nuanced and specialty-level neuromuscular disease knowledge, pediatricians can make significant progress toward establishing an etiology before neuromuscular specialist referral by following these general guidelines.

History

Information obtained through history is extremely valuable. The sex of the child, although obvious, can help eliminate fairly common and potentially devastating causes of weakness, such as Duchenne, Becker, and Emery-Dreifuss muscular

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dystrophies because these are X-linked muscle disorders. A detailed timeline of the weakness is also very helpful. Congenital myopathies and most spinal muscular atrophies can almost be ruled out in children who do not present with weakness until late childhood and who meet their gross motor milestones on time. A family history of muscle disease can be telling because myotonic dystrophy (the most common neuromuscular disorder) and fascioscapulohumeral muscular dystrophy are autosomal dominant. Many limb girdle muscular dystrophies, hereditary sensory motor neuropathies (Charcot-Marie-Tooth [CMT]), and mitochondrial myopathies can be autosomal dominant was well.

A detailed symptom history is also important. Exercise intolerance, cramping, and myalgias may be indicative of difficulties with glycogenosis, such as acid maltase deficiency (Pompe disease) or defective lipid metabolism. Myophosphorylase kinase deficiency (McArdle disease) may present similarly but with myoglobulinurea. A relapsing-remitting course with worsening symptoms toward the end of the day would support a diagnosis of autoimmune myasthenia gravis. Symptoms of neuropathic pain or sensory loss may represent a generalized neuropathy, such as CMT. Weight changes, sleep disturbances, and skin changes may increase suspicion of a thyroid disorder.

Physical Examination

Physical examination is similarly helpful. Facial weakness is characteristic of myotonic dystrophy or fascioscapulohumeral muscular dystrophy. Ataxia on examination indicates ataxic neuromuscular disorders such as Friedreich ataxia. Cavus foot deformities and hammer toes in conjunction with decreased sensation and strength distally suggest CMT or other neuropathy. Grip or percussion myotonia is pathognomonic for myotonic dystrophy. A Gowers sign, although nonspecific, is informative regarding the severity of pelvic girdle weakness and can be seen in dystrophinopathies such as Duchenne, Becker, and limb girdle muscular dystrophies.

Laboratory Screening

A few screening laboratory values will narrow the differential diagnosis of a child presenting with weakness. Creatine kinase is probably the single most important muscle screen. Duchenne, Becker, most limb girdle, and some congenital muscular dystrophies can be effectively ruled out with normal creatine kinase levels. In addition, myotonic dystrophy and some metabolic myopathies can present with elevated creatine kinase levels. Weakness and fatigue may be difficult for children to distinguish in history, so a basic complete blood cell count can be helpful in screening for anemia. Finally, thyroid screening should be ordered on any child who presents with new weakness because thyroid dysfunction is a treatable cause of weakness. Genetic testing, electromyography, muscle imaging, and muscle biopsy are further diagnostics for a neuromuscular specialist to run.

Case Diagnosis and Treatment

The low thyrotropin and elevated T4 levels in our patient raised clinical suspicion for a hyperthyroid condition. The diagnosis was supported by a clinical history of sleep disturbance and weight loss. The cause of hyperthyroid is further elucidated in additional laboratory evaluation, which included thyrotropin receptor, thyroid-stimulating immunoglobulin, and thyroperoxidase autoantibodies. In our patient, all of these assays returned positive, confirming the diagnosis of Graves disease. Graves is an automimmune disorder in which thyrotropin receptor autoantibodies stimulate the thyroid gland to produce both T4 and triiodothyronine (T3), with systemic suppression of thyrotropin production via feedback.

Graves disease accounts for 95% of all cases of hyperthyroidism in children and adolescents, with an overall prevalence of approximately 1 in 5,000. Girls are 5 times more likely to carry the diagnosis than boys. Common symptoms of Graves disease include accelerated growth, stare and lid lag, ophthalmopathy with resulting extraocular muscle weakness, goiter, tachycardia, mitral valve prolapse, tremor, benign intracranial hypertension, hyperhidrosis, and weight stagnation or loss by increased calorigenesis. Children may also suffer in school, likely from a combination of decreased attention, hyperactivity, and poor sleep patterns. Finally, weakness of proximal muscles as well as decreased muscle contraction efficiency and fatigue can be presenting symptoms, as was the case with our patient.

The goal of treatment in Graves disease is to obtain a euthyroid state. Thionamide drugs such as methimazole can be used to inhibit thyroid hormone synthesis. Treatment for at least 18 months has demonstrated some benefit regarding remission. Thyrotropin levels that remain suppressed despite treatment indicate a higher likelihood of relapse. Radioiodine (iodine 131) decreases thyroid hormone production but is not commonly used in children given the radiation exposure risk. Our patient underwent treatment with methimazole 15 mg twice daily with T3 and free T4, and we monitored her thyrotropin levels monthly; the methimazole dose was eventually lowered to 5 mg twice daily.

After 2 months her thyroid function returned to normal levels. At 3-month follow-up she reported improvement in muscle weakness to the point that she felt confident in rejoining her dance team.

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Lessons for the Clinician

- The differential diagnosis for weakness in a child may be broad but can be significantly narrowed with a through history and physical examination.
- Simple screening laboratory tests, such as creatine kinase, complete blood cell count, and thyroid studies, represent a low-cost, high-yield evaluation.
- Although rare, thyroid conditions can contribute to weakness in children and should be investigated.
- Referral to a neuromuscular specialist should be considered after first-line history, physical examination, and laboratory screening are conducted.

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Occult Spinal Dysraphism

Lucy C. Holmes, MD, MPH,*‡ Veetai Li, MD†‡
*Department of Pediatrics, †Department of Neurosurgery, Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY
‡John R. Oishei Children's Hospital, Buffalo, NY

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Spinal dysraphism is an incomplete fusion of the spine during embryologic development and encompasses a spectrum of congenital anomalies that can affect the spinal cord, nerve roots, and vertebral column. These anomalies can be categorized into open and closed spinal dysraphism. Open spinal dysraphism is also known as spina bifida aperta. The neural tissue in these lesions is exposed, and examples include meningoceles and myelomeningoceles. Closed spinal dysraphism is also referred to as occult spinal dysraphism (OSD). In these lesions, the neural tissue is covered with skin, making the diagnosis less apparent. Isolated vertebral defects are the most common and least severe form of OSD. Other examples of OSD include neurenteric cysts, split notochord syndrome, split spinal cord malformation, sacral meningeal cysts, spinal lipomas, caudal regression syndrome, dorsal dermal sinus tracts and cysts, and tethered cord syndrome. Among these diagnoses for OSD, evaluations for potential tethered cord syndrome and dermal sinus tracts are the most common reasons for referrals to pediatric neurosurgeons. Because the scope of this *In Brief* cannot go into detail with all of these diagnoses, we describe tethered cord syndrome and dorsal dermal sinus tracts in more detail and then focus on the epidemiology, associated morbidity, physical findings, challenges with diagnosis, and management of all types of OSD.

Tethered cord syndrome can result from several types of spinal dysraphism. A tethered cord arises when the spinal dysraphic malformation creates a situation where the spinal cord is anchored in some way, thereby causing the spinal cord to stretch as the child grows. This leads to ischemic changes in the neurons. Findings on imaging depend on the type of spinal dysraphism involved, but generally, concern about a tethered cord is heightened if the conus medullaris terminates caudal to the L2 to L3 disc space or if the diameter of the filum exceeds 2 to 3 mm. Children with tethered cord syndrome can develop progressive motor and sensory signs and symptoms, including gait abnormalities, muscle atrophy, abnormal deep tendon reflexes, loss of bladder control, lumbosacral pain, orthopedic deformities of the foot, and scoliosis.

Dorsal dermal sinus tracts are communications between the surface of the skin and deeper tissues. The sinus tracts are lined by stratified squamous epithelium and are associated with lumbosacral dimples or pits. They may terminate in the subcutaneous tissues or extend into the subarachnoid space and attach to the lower spinal cord, resulting in an intradural extension. Intradural extensions place patients at risk for meningitis because bacteria can enter the subarachnoid space via the sinus tract. Dermal sinus tracts may also cause spinal cord tethering when the attached sinus tract anchors the cord in an abnormal way. Although most of these lesions are located in the lumbosacral area, they can also be found in the cervical and thoracic regions of the spine.

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The incidence of all forms of spinal dysraphism (open and closed) is 0.5 to 8 cases per 1,000 live births. OSD is the most common spinal anomaly. The probability of OSD varies by the clinical presentation and is categorized into low-, intermediate-, and high-risk groups. Children with isolated dimples are in the low-risk group for spinal dysraphism. In children with isolated intergluteal dimples, the probability is 0.34%, and in those with isolated lumbosacral dimples the probability increases to 3.8%. The intermediate-risk group includes children with low or intermediate anorectal malformations, who have a 27% and 33% probability of OSD, respectively. The probability increases to 36% in children with a cutaneous lesion such as a hemangioma, hairy patch, or lipoma. These children are also in the intermediate-risk group. The high-risk group includes children with a high anorectal malformation or cloanal malformation, whose probability for OSD is as high as 44% to 46%. One hundred percent of children with cloacal exstrophy also have OSD. In addition, children with 2 or more congenital midline cutaneous lesions have a 61% to 67% risk of OSD.

OSD is typically asymptomatic in infants and young children, although 50% to 80% of patients have cutaneous lesions on examination. Some individuals remain asymptomatic as adults. However, initial findings in those who develop symptoms are insidious and typically involve autonomic and sphincter dysfunction such as urinary retention, incontinence, urgency or frequency, urinary tract infections, or constipation. Later findings involve sensorimotor symptoms, including leg weakness, decreased or increased muscle tone, and decreased sensation in the legs and perineal area. Left undiagnosed, spinal dysraphism can lead to severe and irreversible neurologic, musculoskeletal, genitourinary, or gastrointestinal disease. Early diagnosis and treatment improves outcomes.

OSD is commonly associated with physical findings on the skin overlying the spine such as a hemangioma, capillary malformation, hair tuft, hypopigmentation or hyperpigmentation, nevus, deviation or duplication of the intergluteal cleft, lipoma, skin tag, or dermal dimple or pit. Of children with OSD, dermal dimples and pits are seen in only 3% to 5% of children with physical findings.

Although dermal dimples or pits may represent a dorsal dermal sinus tract or other cause of OSD, they most commonly are incidental findings in infants and children. Coccygeal or intergluteal dimples and pits occur in 2% to 4% of all children. They are found close to the tip of the coccyx and are usually visible only when the gluteal folds are separated. Although dermal dimples most likely represent benign lesions, they may be the only indication of an underlying spinal dysraphism, and so clinicians must decide what associated features would be an indication for imaging to prevent the less common, but significant, morbidity that can be seen with OSD.

Determining whether to perform imaging studies on infants and children with suspected OSD and selecting the imaging studies are important clinical decisions that many pediatricians face. Any child with neurologic, urologic, or orthopedic signs or symptoms should undergo imaging or be referred to a neurosurgeon. Among infants who do require further evaluation, plain radiographs can reveal vertebral abnormalities but will not detect other causes of OSD and so are generally not recommended. Ultrasonography and magnetic resonance imaging (MRI) are the 2 recommended tests for children with more suspicious lesions. Ultrasonography is not recommended after 3 to 4 months of age because ossification of the vertebral arches makes visualization more difficult.

This decision to image a patient with an abnormal skin finding alone can be informed by knowing the associated probabilities of the abnormal skin finding with OSD. Children with isolated coccygeal or intergluteal dimples or pits do not require imaging because the associated risk of having OSD is 0.34%, whereas those with lumbosacral dimples or pits have a 3.8% risk. Children with lumbosacral dimples (located >2.5 cm from the anus) or with lesions that are greater than 5 mm in size should undergo imaging due to their higher probability (3.8% and 23%, respectively) of OSD than children with isolated coccygeal dimples. The recommended imaging test, ultrasonography or MRI, for infants younger than 3 to 4 months whose only physical sign is a lumbosacral dimple or pit is controversial and often institution dependent. Children older than 3 to 4 months with isolated lumbosacral dimples should be evaluated with MRI because ultrasonography is no longer useful after that age. Children with cutaneous stigma other than an isolated dermal dimple or pit, such as hemangiomas, hair tufts, or lipomas, should be evaluated with MRI at any age because they have a 36% probability of OSD. Children with anorectal malformations, cloanal malformation, or cloacal exstrophy have a 27% to 100% risk of OSD and so should be evaluated with MRI.

Infants with evidence of spinal dysraphism on examination or radiologic testing, as well as children with symptoms suggestive of OSD, should be referred to a pediatric

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neurosurgeon for further management. Infants and children with cutaneous lesions along the spine other than a coccygeal dimple or pit can also be referred to a neurosurgeon for further evaluation because these children have a higher risk of spinal dysraphism.

COMMENT: This *In Brief* reminds me of the countless spine examinations I have performed on newborns looking for a dimple or cutaneous lesion, but I am not sure I have always been as vigilant with including this part of the examination with older infants and young children. Infants and young toddlers with OSDs may not have symptoms from urinary or neurologic abnormalities because delay in sphincter control or lower extremity findings may not be readily apparent at their ages. Hence, a careful physical examination of the spine is critical to identify cutaneous physical examination risk factors and patients who warrant further investigation. Concern for OSDs remains the most common indication for spine imaging. Of note, plain radiographs are no longer recommended due to their low specificity of 18% while sensitivity has been found to be 80%. Although there have been no randomized clinical trials evaluating surgery versus medical management in OSD and timing of the surgery, studies to date suggest better outcomes for children who had surgery before 3 years of age. This is an important area where more research is needed to guide our clinical decision making.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

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Congenital Anomalies of the Kidneys, Collecting System, Bladder, and Urethra: 1. E; 2. A; 3. D; 4. B; 5. D.

Ventral Abdominal Wall Defects: 1. A; 2. A; 3. C; 4. E; 5. E.

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Visual Diagnosis

Midline Thoracic Dimple in a 10-month-old Girl

Neha Gupta, MD,* Leyden Standish-Parkin, MD,* Sergey Prokhorov, MD*

**Department of Pediatrics, Lincoln Medical Center, New York, NY*

PRESENTATION

A 10-month-old girl presents to the clinic with a dimple at the level of the midthoracic spine that has been present since birth. The parents do not have any other concerns. Developmental milestones are appropriate for age. The mother reports that there is no discharge from the dimple, motor anomalies, or changes in bowel or bladder pattern.

The patient was born at 33 weeks' gestation by cesarean delivery owing to fetal bradycardia. She had respiratory distress at birth and was treated with nasal continuous positive airway pressure for 1 day. The mother had a history of gestational diabetes, poorly controlled with insulin.

On physical examination, her temperature is 98.8°F (37.1°C), heart rate is 134 beats/min, and respiratory rate is 32 breaths/min. She has a dimple over the T5 spinous process; it is a very small opening without erythema or discharge (Figs 1 and 2). Mental status is appropriate for age, and no facial asymmetry or weakness is noted. She has normal sensory response to touch, normal motor examination findings with normal bulk and tone in arms and legs, and no nystagmus. She is able to crawl and has normal reflexes with absent clonus.

Laboratory studies demonstrate normal complete blood cell count, comprehensive metabolic panel, and coagulation studies. Ultrasonography of the spine reveals a 3-mm cystic round lesion in the superficial soft tissues overlying the T5 vertebral body. Magnetic resonance imaging (MRI) confirms the diagnosis.

DIAGNOSIS

An MRI demonstrates an 8-cm loculated cystic lesion in the posterior aspect of the upper thoracic spine compressing the spinal cord, within the dura mater. It also shows a small dermal sinus tract extending from the skin surface to a cystic subcutaneous mass superficial to the muscular fascia at the T6 level. A 1-cm posterior midline cyst at the T4-5 level outside the dura mater is also seen. No bony defect is identified (Fig 3).

DISCUSSION

Spinal congenital dermal sinuses (SCDSs) are a very rare form of spinal dysraphism. They are cutaneous depressions or tracts that extend inward from the skin surface and connect the body surface with the central nervous system or its coverings. The incidence is reported to be approximately 1:2,500 live births. (1)

AUTHOR DISCLOSURE Drs Gupta, Standish-Parkin, and Prokhorov have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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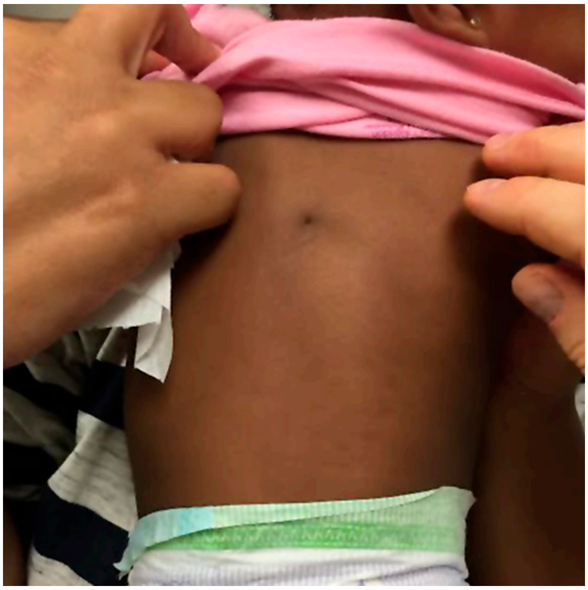

Figure 1. A dimple in the midline of the back of a 10-month-old girl at the level of the midthoracic spine with a very small opening.

Formation of the spinal cord occurs by disjunction of the neuroectoderm during neurulation. (2)(3)(4)(5)(6) Failure of this disjunction results in the formation of SCDSs. They may be associated with inclusion tumors (dermoid, epidermoid, teratoma), tethered cord, myelomeningocele, lipomeningocele, or bifid spine. (2) Associations of dermal sinuses can vary by their location; for example, midline dermal sinuses are usually associated with dermoid cysts, whereas those adjacent to the midline are associated with epidermoid cysts. (7)(8) Inclusion of the embryologic ectodermal crest cells in the neural epithelium during neural tube closure results in the formation of a dermoid cyst. (9)(10) They are usually located in the lumbar (41%) and lumbosacral (35%) regions but can also be present in the thoracic (10%) and cervical (1%) sites. (11)

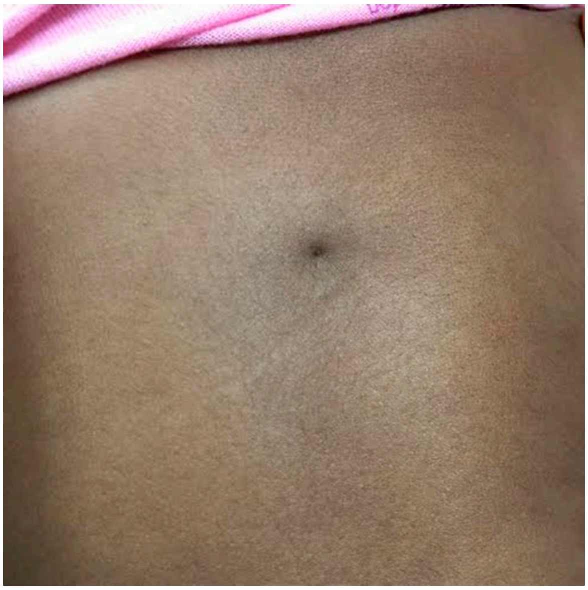

Figure 2. Close-up of a midline dimple on the back of a 10-month-old girl.

Lining the dermoid cysts is stratified squamous epithelium, and they may contain dermal adnexa, including hair follicles, sweat glands, and sebaceous glands. (12) Dermoids can be located in the spinal canal, either outside the spinal cord (63%) or within the spinal cord (38%). (13)(14) Dermoid cysts usually present in the second or third decade of life and account for less than 1% of congenital spinal tumors. (7)(14) They have a very slow growth rate and can attain a large size without causing any signs or symptoms. (2) In the presence of a dermal sinus, patients usually present early in the first decade due to sinus discharge and infection. (13)(15)

Dermal sinuses usually present at a young age with skin findings, neurologic deficit or infection. A dimple in the midline, on either the skull or the back of the spine, is a common finding in these patients. Other cutaneous findings include skin tag, angioma, hypertrichosis, lipoma, and abnormal pigmentation. (16) Some patients may have symptoms secondary to local infection of the cyst characterized by erythema or induration. (16) Patients can also present with a neurologic deficit because of a tethered cord, an abscess, or by compression of neural structures, an associated dermoid, or epidermoid tumor. (13) Dermoid cyst can rupture spontaneously, resulting in ventriculitis and chemical meningitis, which can lead to acute worsening of neurologic deficit. (15) Raised intracranial pressure and hydrocephalus have also been associated with these tumors. (17)

Two-view radiographs of the spine may demonstrate dysraphic changes such as laminar defects, (5) but MRI is the diagnostic study of choice. The appearance of a dermoid cyst on MRI is variable and most commonly shows low-to-intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images. (18) In most cases, it can also reveal the sinus tract along with any other associated pathology.

Total microsurgical excision of the dermoid cyst along with the sinus tract and the dimple is the treatment of choice. Partial excision of the dermoid cyst wall with decompression can also be performed if there is a dense adhesion of lesion with the spinal cord. (19) Conservative management of asymptomatic SCDS is not recommended.

Prompt diagnosis and surgical management decreases the risk of complications, including meningitis, abscess

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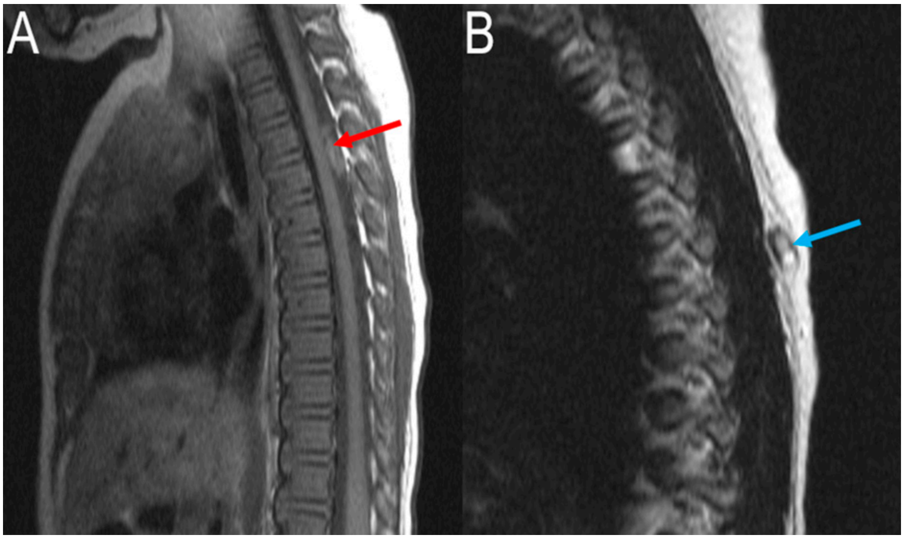

Figure 3. Sagittal T1-weighted magnetic resonance images of the thoracic spine. A. An 8-cm hypointense cystic mass extends from C7 to T8-9 with a presumed small foci of hemorrhage (red arrow). The spinal cord is displaced anteriorly. B. A small sinus tract extends from the dermis to a cystic subcutaneous mass superficial to the muscle fascia at the T6 level (blue arrow).

formation, and tumor growth, that may increase the difficulty in resection or lead to cord compression and long-term neurologic deficit.

PATIENT COURSE

The patient underwent resection of the mass without any complications. The pathology report described a dermal sinus tract measuring 3.2×1.8×1.0 cm. Also identified was a thoracic dermoid tumor described as a 2.8×0.5×0.3-cm epidermal inclusion cyst containing pilosebaceous units with surrounding nodular fibroadipose tissue, consistent with monodermal teratoma. The excised cyst was smaller than seen on the MRI. This discrepancy in size could be due to the flow of surrounding cerebrospinal fluid around the cyst, giving an impression that the cyst is larger than its actual size. In a follow-up appointment, the patient had a normal neurologic examination with no focal deficits.

Summary

- Spinal congenital dermal sinuses should be suspected in all patients with midline cutaneous findings such as a dimple in the midline of the spine.
- Even in asymptomatic patients with dermal sinus, there should be a high index of suspicion of associated tumors.
- Prompt imaging and timely surgical removal of the sinus should be performed to preserve neurologic function and prevent complications.

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